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Complete List of Authors:	Ampt, Frances; Burnet Institute; Monash University, Department of Epidemiology and Preventive Medicine Mudogo, Collins; International Centre for Reproductive Health Kenya Gichangi, Peter; International Centre for Reproductive Health Kenya; University of Nairobi Lim, Megan; Burnet Institute; Monash University, Department of Epidemiology and Preventive Medicine Manguro, Griffins; International Centre for Reproductive Health Kenya Chersich, Matthew Jaoko, Walter; University of Nairobi Temmerman, Marleen; Aga Khan University - Kenya; International Centre for Reproductive Health Laini, Marilyn; International Centre for Reproductive Health Kenya Comrie-Thomson, Elizabeth; Burnet Institute; Monash University, Department of Epidemiology and Preventive Medicine Stoové, MA; Burnet Institute, Agius, Paul; Burnet Institute; Monash University, Department of Epidemiology and Preventive Medicine Hellard, Margaret; Burnet Institute L'Engle, Kelly; University of San Francisco Luchters, Stanley; Burnet Institute; International Centre for Reproductive Health
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WHISPER or SHOUT study: Protocol of a cluster-randomised controlled trial assessing mHealth sexual reproductive health and nutrition interventions among female sex workers in Mombasa, Kenya

Frances Ampt*[1,2], Collins Mudogo*[3], Peter Gichangi[3,4,7], Megan Lim[1,2], Griffins Manguro[3], Matthew Chersich[5], Walter Jaoko[4], Marleen Temmerman[3,6,7], Marilyn Laini[3], Liz Comrie-Thomson[1], Mark Stoové[1], Paul A. Agius[1,2,8], Margaret Hellard[1], Kelly L'Engle[9], Stanley Luchters[1,2,7]

Affiliations:
1. Burnet Institute, Australia
2. Department of Epidemiology and Preventive Medicine, Monash University, Australia
3. International Centre for Reproductive Health (ICRH), Kenya
4. University of Nairobi, Kenya
5. Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, South Africa
6. Aga Khan University, Kenya
7. International Centre for Reproductive Health (ICRH), Department of Obstetrics and Gynaecology, Ghent University, Belgium
8. Judith Lumley Centre, La Trobe University, Australia
9. University of San Francisco, USA

* both authors contributed equally to the manuscript.

Corresponding author: Associate Professor Stanley Luchters
Stanley.luchters@burnet.edu.au

Abstract

Introduction: New interventions are required to reduce unintended pregnancies among female sex workers (FSWs) in low- and middle-income countries, and to improve their nutritional health. Given sex workers' high mobile phone usage, repeated exposure to short message service (SMS) could address individual and interpersonal barriers to contraceptive uptake and better nutrition.

Methods: In this two-arm cluster randomised trial, each trial arm constitutes an equal-attention control group for the other. SMS messages were developed in a systematic, participatory and theory-driven manner, and cover either sexual and reproductive health (WHISPER) or nutrition (SHOUT). Messages were sent to participants 2-3 times/week for 12 months, and include fact-based and motivational content, and role model stories. Participants can send reply texts to obtain additional information. Sex work venues (clusters) in Mombasa, Kenya, were randomly sampled with a probability proportionate to venue size. Up to 10 women are being recruited from each venue, to a total sample of 860. FSWs aged 16-35 years, not currently pregnant and who have a mobile phone, are eligible. Structured questionnaires, urine pregnancy tests, HIV and syphilis rapid tests, and full blood counts will be performed at enrolment, six and twelve months.

Analysis: The primary outcome of WHISPER is unintended pregnancy incidence, and of SHOUT prevalence of anaemia at 12 months. Each will be compared between study groups using discrete-time survival analysis.

Potential limitations: Contamination may occur if participants discuss their intervention with those in the other trial arm. This is mitigated by cluster recruitment and only enrolling a small portion of all clusters.

Conclusions: The design allows for the simultaneous testing of two independent mHealth interventions, for which messaging frequency and study procedures are identical. This trial may guide future mHealth initiatives and provide methodological insights into use of reciprocal control groups.

TRIAL REGISTRATION:

Australian New Zealand Clinical Trial Registry: ACTRN12616000852459

STRENGTHS AND LIMITATIONS OF TRIAL DESIGN

Strengths of the study include:

1. Use of a cluster-RCT with reciprocal controls allows for the simultaneous testing of two mHealth interventions, for which message frequency and study processes are identical; only the content of the messages differs.
2. Testing two independent hypotheses simultaneously is efficient, using considerably fewer resources than needed for two independent trials.
3. The design mitigates biases from unequal attention in trial groups (i.e., participants in both groups have comparable interaction with the study team), positive expectations, and non-blinding.[1 2]

Important limitation of the study are:

1. The potential for contamination may arise if women receiving SRH messages share them or discuss their content with women in the nutrition arm, and vice versa. Contamination would diminish the ability to detect a difference in effectiveness between the two groups. Cluster-based intervention allocation has been used to reduce the potential for contamination between individuals; though FSWs often work from multiple venues, so may come in contact with participants from other clusters. Also countering this limitation, we are recruiting only a small portion of sex workers across a large geographic area (up to 106 of 760 hot spots, and 860 of an estimated 8,516 FSWs), which diminishes the chances of interaction between trial arms. Lastly, we will attempt to measure contamination by asking about message sharing in the questionnaire.
2. A further potential limitation of this design is that the outcomes of the interventions may interact. While the two health domains were chosen due to the minimal overlap between behaviours, there are some plausible points of influence between the arms. For example, higher rates of pregnancy in the nutrition arm may lower haemoglobin and iron levels in these women. More generally, those receiving messages on one aspect of health may improve their health behaviours in multiple health domains, potentially diluting the effect measures of the comparison between the study arms.
3. It is also important to note that the SRH intervention aims to increase demand for contraceptives, and that translating demand into raised coverage may be limited by deficiencies in the health system (supply-side issues). These may include commodity stock-outs, insufficient choice of methods offered to women, and discriminatory treatment of FSWs by health workers.[3,4] Supply-side issues may also influence outcomes in the nutrition group, for example, if a limited range of foods is available in the area.
4. Although nutrition messages may alter knowledge and attitudes, women's socio-economic conditions may preclude a change in diet and thus in nutritional markers such as haemoglobin.

5. The use of both push and pull technologies is a novel and potentially powerful approach, however their simultaneous use may make it difficult to determine the size of their independent effects. We will perform a dose-response sub-analysis to examining whether differential exposure to messages (pull or push) is associated with the trial outcomes.

INTRODUCTION

Female sex work

Despite sex work being very common in sub-Saharan Africa, with one in twenty women estimated to have exchanged sex for money, goods or other favours,[5] it remains a highly stigmatised and mostly criminalised practice, including in Kenya.[5 6] The hostile politico-legal and social environment limits sex workers access to health services, especially for sexual and reproductive health (SRH), and for preventing and treating HIV and other sexually transmitted infections(STIs).[7] Strategies such as providing peer education and outreach services are often unable to overcome the myriad of structural, personal and financial challenges that female sex workers (FSWs) face.[8] This complex situation calls for new interventions that complement the current package of services, and that together improve health and social outcomes for sex workers.

Unintended pregnancies among female sex workers

In many low-income countries, increased provision of low-cost contraceptive methods has raised contraception coverage in the general population,[9 10] but such gains remain inequitably distributed within countries,[11] and they have not translated into improvements for FSWs.[12] This is due to a combination of *individual* barriers to uptake, such as side effects of some contraceptive methods that impact sex work, and myths and misconceptions about particular methods;[13 14] *interpersonal* barriers, including peer norms and pressure from partners not to use contraception,[12] and *structural* barriers, such as stigmatising treatment of FSWs by the health system.[15] Most programs established to improve the health of FSWs primarily focus on HIV and other STIs, and overlook FSWs' broader reproductive needs.[12 16 17] A systematic review of SRH projects aimed at FSWs in Africa found that only a small minority provided pregnancy testing or contraceptive services other than condoms, and few specifically promoted dual method use (the concurrent use of condoms and another effective contraceptive method).[18]

Available data indicate that use of contraception other than condoms by FSWs in sub-Saharan Africa is variable, but generally low, ranging from around 15 to 50%.[12 19-21] Dual method use is rarely measured, but estimated at 10% in one study in Mombasa, Kenya.[12] The most popular modern method, injectable progestin[22] is

prone to discontinuation and contraceptive failure due to incorrect use.[23 24] In contrast, highly effective and low maintenance long-acting reversible contraceptives (intrauterine devices and subdermal implants) are under-utilised, with only 7% of a sample of FSWs in Mombasa having ever used these methods.[12]

While few studies have specifically aimed to measure unintended pregnancy among FSWs, HIV prevention studies among FSWs have reported unexpectedly high rates of pregnancy, with 12-month cumulative incidence of 24% in Kenya,[12] 23% in Madagascar,[20] 27% in Rwanda[25] and 23% in the Caribbean.[26] Unintended pregnancy exposes women to significant health and social risks, such as unsafe (and often illegal) abortion, high maternal and infant morbidity and mortality for those who continue with the pregnancy,[27] and increased financial dependency on sex work, which in turn increases their risk of HIV, other STIs, violence and repeat pregnancies.

Nutrition and nutritional status among female sex workers

Urban food insecurity is a growing public health problem in sub-Saharan Africa, and disproportionately affects poor populations, who are more exposed to nutritional risks and have less capacity to adopt effective coping strategies.[29] As a result of rapid urbanization in low- and middle-income countries - and associated changes in diet leading to overreliance on non-home prepared food that tends to be high in energy, sugar and salt and low in nutrients - under-nutrition and micronutrient deficiencies are increasingly occurring alongside over-nutrition, overweight and obesity.[29-31] Both under-nutrition and over-nutrition are risk factors for poor health and mortality globally.[32] In women of reproductive age, micronutrient deficiency leads to increased pregnancy complications, and child and maternal morbidity and mortality.[33] Anaemia, predominantly caused by iron deficiency, is endemic among women in sub-Saharan Africa; in Kenya, 36% of pregnant women and 25% of non-pregnant women are estimated to be anaemic.[34]

While there are no published data on malnutrition among FSWs in Kenya, lack of physical activity, chaotic lifestyles and poor diet are factors which are likely to increase the susceptibility of FSWs to unhealthy weight gain, while at the same time contributing to their risk of micronutrient deficiency. Equally, food insecurity and hunger have been identified as key push factors for women to initiate and continue sex work.[35 36] In one study of sex workers in the Lagos metropolitan area in Nigeria, 35% of respondents had entered sex work as a coping strategy in response to food insecurity.[37]

mHealth interventions

Mobile phones have the potential to effectively engage FSWs, provide information, improve knowledge and address individual and interpersonal barriers to contraception use and nutritional health. Mobile phone coverage is over 80% in Kenya,[38] and close to ubiquitous among FSWs, who constitute a large mobile

population that relies on mobile phones for maintaining social and business networks (unpublished formative research from Mombasa). mHealth interventions allow for repeated, theory-driven, user-centred, and low-cost exposure which is known to be important for securing behaviour change.[39]

Short messaging service (SMS) technology has been shown to impact health behaviour in a number of systematic reviews on the topic.[40-43] There are, however, few randomised-controlled trials (RCTs) addressing SRH behaviour through SMS.[44-46] Two trials in Australia demonstrated improvements in health-seeking behaviour and sexual health outcomes, particularly among young women.[45 46] Non-randomised trials and program evaluations have also had positive findings.[47 48] With regards to nutrition, trials in the USA and Iran have demonstrated the efficacy of SMS for changing eating behaviours[49] and knowledge and attitudes towards iodine consumption,[50] respectively. SMS interventions targeting over-nutrition have also been tested,[51-55] some of which significantly impacted on weight reduction.[51-53]

Overall, research is failing to keep up with the rapid proliferation of mHealth interventions.[42] Despite the potential gains, there remains a lack of rigorous research that evaluates SRH promotion initiatives in LMICs,[56] and within the field of nutrition the lack of rigorous data is even more pronounced. Furthermore, among populations like FSWs from low-resource settings, who tend to have lower health knowledge and fewer resources for obtaining health information, intervention impact may be greater than that observed in high-income countries.

WHISPER and SHOUT interventions

The Women's Health Intervention using SMS for Preventing Unintended Pregnancy (WHISPER) study was developed in response to the substantial SRH needs of FSWs in Kenya, the potential gains offered by increasing demand for family planning among FSWs through mHealth, and the research gaps in this field. If found to be effective, mHealth for SRH could be added to the current service packages provided for sex workers, complementing and supporting the effectiveness of these services.

Similarly, the need to improve nutrition for women in poor and vulnerable settings, and the paucity of data on FSWs' nutritional health, led to the development of the SMS intervention to improve nutritional Heath OUTcomes (SHOUT). The SHOUT trial will provide important preliminary data on this under-investigated issue, and explore whether mHealth can offer an effective means of addressing malnutrition and anaemia in this population.

This paper presents the protocol for the WHISPER or SHOUT study, which commenced in September 2016. Recruitment is anticipated to continue until June 2017, and 12-month data collection to finish in June 2018.

METHODS AND ANALYSIS

This is a two-arm cluster-RCT, which will examine the effectiveness of two parallel interventions (addressing SRH and nutrition respectively) delivered via mobile phone among FSWs in Mombasa, Kenya. As each intervention addresses a unique set of specific issues, and the mode of delivery and level of exposure is the same, each trial arm serves as an appropriate reciprocal control group for the other.[1]

Study objectives and outcomes

The overall aim is to improve the health and wellbeing of female sex workers in resource-constrained settings. Specifically, the study will assess the effectiveness of two independent 12-month mobile phone-delivered interventions in improving:

i) SRH outcomes for FSWs receiving the WHISPER intervention, compared to women receiving a nutrition intervention; and

ii) nutritional status for FSWs receiving the SHOUT intervention compared to women receiving an SRH intervention.

The feasibility and acceptability of the interventions will also be assessed, using a combination of quantitative methods (structured questionnaires at six and 12 months) and qualitative methods (in-depth interviews at 12 months).

WHISPER

The primary study outcome for WHISPER is the incidence of unintended pregnancy over 12 months of follow-up. Unintended pregnancy is defined as pregnancy that is mistimed, unplanned, or unwanted at the time of conception.[57] Women in the study are asked about their pregnancy intentions for the forthcoming six months at enrolment, and at the six and 12 month visits. A psychometrically-validated 6-item questionnaire (London Measure of Unintended Pregnancy) will also be used to score pregnancy intention in cases where pregnancy occurs during study follow-up.[58] Pregnancy events are defined as either a positive result on urine pregnancy screening at the six or 12 month visits (or at unscheduled visits should these occur), or a self-reported pregnancy that has occurred between study visits.
Secondary outcomes will be measured at baseline and six and 12 months, and include incidence of HIV and syphilis measured by point-of-care testing, and self-reported SRH knowledge, behaviour and service utilisation (assessed by structured questionnaire).

SHOUT

The primary study outcome for SHOUT is the prevalence of anaemia at 12 months of follow-up. This outcome is measured using a certified laboratory-based haematology machine at baseline and 12 months, and is defined as haemoglobin level below 12.0g/dL, consistent with the World Health Organisation definition).[34] A point-of-

care haemoglobinometer will also be used to enable immediate management of anaemia, but the laboratory measure will be used to calculate the primary outcome. Secondary outcomes include mean haemoglobin (Hb) levels at 12 months, prevalence of malnutrition (measured by anthropometry at baseline and six and 12 months), and self-reported nutritional knowledge and behaviour (assessed by structured questionnaire at baseline and six and 12 months).

Study intervention

Development of WHISPER or SHOUT study interventions

Changes in attitudes and behaviours are most likely to occur when communication interventions are theory-driven, interactive and follow best practice in design and implementation.[59] Furthermore, sustainable positive behaviour change among individuals and communities occurs as a process, supported by carefully designed interventions, and not as a single event.[60 61]

The WHISPER and SHOUT interventions were therefore developed following a pre-defined protocol and in a systematic and participatory manner, ensuring that the intervention was grounded in evidence, was relevant and acceptable to the study population, and followed a logical process of behaviour change based on staged and social cognitive theoretical approaches.[62] An extensive review of the literature and consideration of health behaviour change theory informed the development of logic models for both study arms (figures 1 and 2), and the subsequent drafting of messages. Participatory and user-centred design and testing of the mobile phone intervention[63-65] was conducted with the target population in four informal consultative meetings, 12 formal workshops and 24 usability testing interviews. FSWs were involved in identifying important issues that affect them, developing messages and role model stories, reviewing and refining the content, and suggesting changes to the intervention architecture.

Structure and delivery of the intervention

Both the SRH and nutrition intervention consist of SMS (text) messages sent to participants two to three times per week for 12 months.

This includes the following components:

- 'Push' texts covering the main content domains, providing simple information, motivational messages and strategies to prompt action;
- 'Role model stories' about FSWs modelling healthy social norms and sent in 4-5 instalments in one month (alternating months with stand-alone messages);
- A 'pull', or on-demand menu that participants can access by texting into the system to obtain more information on high-priority topics and local services.

The intervention is being delivered by the VOTO mobile (https://www.votomobile.org/) online platform. All messages are loaded onto the system in a pre-determined order and sent automatically to each cluster of participants at the scheduled time (calculated from each cluster's start date). Participants are able to text assigned codes at any time during the study to access the pull messages, with SMS costs incurred by the study (no charge for participants). Content is only accessible to enrolees in the relevant intervention group, so that those in the nutrition arm cannot directly access SRH messages, and vice versa.

Table 1: Number, length and timing of messages for each study arm

Message type	Number of messages	Length	Timing
Push messages	82 (both arms)	Up to 160 characters (1 SMS 'screen')[1]	3 per week (Monday, Wednesday and Saturday mornings) during months 1, 3, 5, 7, 9, 11, 13[2]
Push interview reminders and study information	7 (both arms)	160 – 480 characters (1-3 screens)	
'Alerts': push messages linking participants to the pull system	19 (SRH); 18 (nutrition)	160 - 320 characters (1-2 screens)	
Role model stories (push messages)	26 (SRH); 27 (nutrition) (covering 6 stories for each arm)	160 – 640 characters (1-4 screens) per message	2 per week (sent Monday and Friday mornings) during months 2, 4, 6, 8, 10, 12
Pull (on-demand) messages	80 (SRH); 49 (nutrition)	160 – 640 characters (1-4 screens)	User determined

Table 1 presents a summary of the structure of the interventions, showing that the interventions are essentially equivalent in all structural components except the on-demand system. This discrepancy is due to additional pull messages in WHISPER which provide information about SRH services, allowing participants to link in with local sex worker-sensitive providers. This was deemed important on ethical grounds given the sensitive content of the WHISPER intervention, and because promotion of contraception can only impact pregnancy rates if delivered alongside accessible services that provide the methods in question.

In contrast, the promotion of healthy eating does not require an intermediate service utilisation step to result in improved nutritional outcomes. Furthermore, low-cost or free nutrition services are not widely available in Mombasa, and screening asymptomatic non-pregnant women for anaemia is rarely practiced, so we were unable to reliably list relevant services for SHOUT.

[1] Messages are charged per 160 characters (1 screen). Messages longer than this will appear as 1 long SMS on most phones, but may be split into multiple messages on older phones.

[2] There are 13 blocks of 4 weeks each, making up 12 calendar months in total.

Setting and participants

Eligible women are recruited from mapped sex work venues by well-established peer outreach workers. Sex work venues consist of fixed-site businesses including nightclubs, bars, brothels and hotels, as well as public spaces such as street corners and beaches, where sex is known to be bought and sold. The study is conducted in two areas of Mombasa, a major economic centre in Kenya and East Africa, with busy port, rail and industrial enterprises. The local implementing partner, International Centre for Reproductive Health (ICRH; a WHO Collaborating Centre for Reproductive Health in Mombasa) has a research track record in the area dating back to 2002, including many trials and other prospective intervention studies with FSWs[66-68] and numerous non-interventional studies.[69-72]

Inclusion and exclusion criteria

To be eligible for participation, women must: 1) be aged 16 to 35 years; 2) self-report having engaged in sex work (received money in exchange for sex) at the site of recruitment in the last six months; 3) not currently be pregnant or planning pregnancy within 12 months; 4) currently reside, and plan to continue residing within the study area for the next 12 months; 5) have a personal mobile phone with Safaricom or Airtel subscription, and be willing to provide the phone number to the researchers to receive the intervention messages; 6) self-report to be SMS literate (i.e., to be able to read text messages in English); 7) be willing to return for follow-up after six and 12 months; 8) be willing to provide contact information (e.g. home address) to be contacted or visited by a member of the research team in the community to remind them to re-attend follow-up visits; and 9) be able and willing to give written informed consent for enrolment in the study.

Exclusion criteria include participation in another mHealth intervention study or in the formative research for this study, and having a medical or non-medical condition detected through screening that hinders study participation, as confirmed by the local Principal Investigator.

Randomisation and sampling strategy

ICRH and collaborators, conducted a two-stage geographic mapping and enumeration exercise of FSWs in 2014, estimating that 11,777 (range 9,265-14,290) FSWs operate from 1053 venues across four sub-counties of Mombasa County.[64] We are recruiting FSW from two of these areas: Changamwe (where an estimated 3,435 FSWs work from 285 venues) and Kisauni (where an estimated 5,081 FSWs work from 475 venues).[64]

A two-stage sampling process has been adopted, drawing on this sampling frame. At the first stage, FSW venues were selected with a probability proportionate to the enumerated size of the sex worker population at the venue, and randomised to either control or intervention arms. Each venue is considered to be a separate

cluster. At the second stage, 10 FSWs are consecutively selected from each venue, based on an estimated mean cluster size of 11.[64] At venues where less than 10 FSWs are active, all FSWs from the selected venue are invited to participate in the study. Sampling of FSW venues will continue until the required sample size of 860 women is achieved.

Cluster randomisation was done centrally by the statistician and prior to recruitment commencing, with an equal number of clusters in both arms. Participants and study team are blinded to intervention and control allocation until after cluster enrolment is completed and all baseline questionnaires administered for that cluster.

Overall, our approach aims for optimal (as random as possible) sampling from the FSW population, while minimising the potential intervention dilution effects of message sharing that might occur with individual-level randomisation.

Recruitment and enrolment

Community mobilisers and peer educators employed by the study apply minimum pre-screening at the site of recruitment to identify potential study participants. Potentially eligible women receive a card with a unique, anonymous *referral card number* (made up of cluster number and sequential participant number for that cluster). They are requested to go to the nearest study clinic for full eligibility screening, consenting and enrolment within the next three days. The study clinics are embedded in existing facilities: an ICRH-run sex-worker drop-in centre in Kisauni and a municipal community health centre in Changamwe. The number of sex workers approached and referral cards disbursed at each cluster are documented, as well as reasons for ineligibility at pre-screening.

Volunteers must bring their referral card number with them to undergo the screening process to ensure that only volunteers selected by the random sampling process are enrolled. Women who consent for participation and successfully complete full screening have their study identification number assigned and are then formally enrolled.

Data collection

Study visits are conducted at enrolment and after six and 12 months at the study clinics. All study staff, including clinicians, research assistants, community mobilisers and peer educators, were trained in the study procedures via a five-day workshop and undertake additional targeted sessions where required.

Procedures for the enrolment visit include collecting informed consent, administering the baseline questionnaire, and performing clinical examination, urine pregnancy test, point-of-care blood tests for HIV, syphilis, and Hb level, and venepuncture for full blood count (haemogram; includes Hb, haematocrit, mean cell volume and white blood count). Follow-up assessments are presented in Table 2.

Table 2: Schedule of assessments for the WHISPER or SHOUT trial

Assessments	Month 0	Month 6	Month 12
Structured questionnaire	✔	✔	✔
Clinical examination	✔	✔	✔
Urine pregnancy testing	✔	✔	✔
Point-of-care HIV and syphilis testing (including pre- and post-test counselling)	✔	✔	✔
Hb measured by haemoglobinometer	✔		✔
Full blood count	✔		✔
In-depth interviews (subgroup of participants from SRH arm)			✔

Questionnaires were developed in English and translated into Swahili, and were based on previously validated measurement tools wherever possible. The baseline questionnaire captures detailed socio-demographic information including education, literacy, employment, income, family and living circumstances, health and illness, and sex work history. SRH enquiry covers previous pregnancy(ies); six-month pregnancy intention; contraception and condom use (including dual protection); reasons for discontinuation or non-use of contraception; contraceptive self-efficacy; sexual and reproductive health seeking and service utilisation; sexual risk behaviours; SRH knowledge and attitudes; relationship control and joint-decision-making with non-paying emotional partners. Participants are asked about whether they have recent STI-related symptoms, which are classified and treated as per syndromic STI guidelines.[73] Nutrition questions gather data on nutrition-related health seeking and service utilisation; food- and hygiene-related knowledge and behaviours; dietary intake and preparation; and food purchasing.

Clinical examination is performed by study clinicians, and includes STI syndromic management and anthropometric measurements to assess nutritional status (i.e. weight, height, waist circumference, hip circumference and mid upper-arm circumference).

The results of rapid diagnostic tests are communicated to the participants at the time of the visit. Participants newly diagnosed with HIV are referred for treatment at specialised centres. Those with positive TPHA are treated with benzathine penicillin at the study visit. Participants with anaemia receive one month of iron and folic acid supplementation, along with a referral to a health facility for follow-up.

Following enrolment, each participant is registered in the VOTO online platform. No identifying details apart from mobile phone number are entered. Intervention allocation is performed by data management staff independent of the study team, and occurs after enrolment is completed for each cluster.

The intervention commences simultaneously for all participants of one cluster in the week following completed cluster-level enrolment (this corresponds to day one, when the first message is sent).

DATA ANALYSES

Analysis of primary endpoints

Primary analysis for WHISPER and SHOUT will compare the primary endpoints (unintended pregnancy incidence and anaemia prevalence respectively) between groups at 12 months. The data analysis team will be blinded to the allocation of participants. Given the interval-censored nature of unintended pregnancy incidence, discrete-time survival models using generalised linear modelling will be used to compare unintended pregnancy incidence between the two trial arms. Comparison of differences in prevalence of anaemia between study arms will be undertaken using multi-level generalised linear modelling

These analyses will, where appropriate, provide estimates with robust standard errors for FSW venue clustering. Standardised probability weighting will be applied in population-averaged analyses to account for any sampling bias where achieved sample cluster sizes vary. Also, where randomisation is not effective in removing allocation bias, adjusted models will be specified. In all analyses, associations will be considered statistically significant at the 5% level.

Sample size

The sample size was calculated to obtain sufficient power to examine the effects of the SRH intervention. Based on a 12-month incidence of unintended pregnancy of 24% in the control group (data from previous research in the study population),[12] enrolment of 860 participants from a minimum of 86 FSW venues would detect a relative reduction in annual unintended pregnancy incidence of 37% (hazard risk=0.63), at 80% power and 5% significance level. This estimate is adjusted for an expected 10% attrition rate (based on previous experience with this population[12]) and an estimated inflation in standard error due to cluster randomisation (design effect=1.18; estimated intra-cluster correlation coefficient (ICC)=0.02, with a cluster size of 10.[74]

Sample size could not be reliably calculated for the SHOUT trial as estimates of anaemia in the local sex work population are not available. However, if we assume a prevalence of 25% (as per the nationally estimate for non-pregnant women[34]), the calculated sample size of 860 would allow for detection of an approximate 42% reduction in odds of anaemia prevalence, with inflation in standard error and attrition rate adjustments applied as above.

ETHICS AND DISSEMINATION

Written informed consent will be obtained from every study participant. Women aged 16 and 17 years are considered mature minors, and able to consent without involving parents and guardians, due to the sensitive nature of the subject matter. Informed consent forms are available in both Kiswahili and English, and describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Most importantly, we are aware of the risk that others seeing the messages may infer that the participant is a sex worker. It is important to mitigate this risk of unintentional disclosure of sex work status and consequent stigma or other adverse events for participants[75]. We will counsel participants about the need for care to be taken to ensure that others do not have access to their phones. The study team will also ask that participants report instances of unintentional disclosure. Such reporting will allow us to provide support to the women concerned and through understanding the events surrounding the case try find ways of avoiding future occurrences.

Ethical approvals have been obtained for protocol version 1.2, dated 22 August 2016 from the Australian Monash University Human Research Ethics Committee (MUHREC - CF16/1552 - 2016000812) and the Kenyan Kenyatta National Hospital, University of Nairobi Ethics and Research Committee (KNH-UoN ERC – KNH-ERC/RR/493).

Several dissemination activities are planned, including to health workers and the district office; the Kenya national policy makers; local and international conferences; and academic publications.

DISCUSSION

Potential impact and significance

The WHISPER study responds to the pressing need for effective and evidence-informed interventions to prevent unintended pregnancies among vulnerable women in resource-constrained settings. Persistent unmet need for family planning contributed to inadequate progress towards reducing child mortality and improving maternal health (Millennium Development Goals 4 and 5), and to the need for the 2010 Global Strategy for Women's and Children's Health.[11] The ability to decide upon the number and timing of children, free from coercion and violence, is a fundamental human right. During the 2012 London Summit on Family Planning,[76] the Kenyan Government committed to increasing funding and contraception coverage by 2015. Despite this supply-side commitment, questions remain about the optimum mechanism to increase demand, particularly among marginalised populations. The WHISPER trial will assess an innovative, sustainable and scalable approach to address some of these gaps.

Study outcomes will be used to inform future policies and public health interventions aimed at increasing uptake of family planning, as well as other SRH

services, among vulnerable populations in a range of similar settings, particularly in LMICs. The rigorous research design and extensive local experience of our team will support advocacy and guide mobile technology services for health promotion as outlined in the 2010 Kenyan Government's Family Planning Guidelines.[77] If found to be effective, this intervention could be sustainably scaled-up across East Africa.

With regards to nutritional health, there are renewed efforts to design and implement action-oriented research, however the role of mHealth in these initiatives remains uncertain.[78] The SHOUT study will go some way towards clarifying whether SMS technology provides a new way of responding to a long recognised, but poorly characterised and long neglected problem. Indeed, if shown to be effective in this trial, mHealth could be incorporated into broader nutrition strategies for FSWs in Africa and elsewhere, and has the potential to be scaled up for use with other women at a population level.

The innovative approach taken by the proposed interventions has never been used to prevent unintended pregnancies or improve nutrition among key risk populations in LMICs. A similar methodology in which SRH text messages were compared to a control SMS intervention has been adopted in Australia with a sun-safety control group,[45] and in the USA with a nutrition control group;[48] although the latter did not measure nutrition outcomes, unlike our trial. This trial will thus set standards for the mHealth field in LMICs, for both interventions and trial methodology. Lessons learnt about optimising SMS technology for both WHISPER and SHOUT could have considerable impact in Kenya, and similar countries, for a range of health priorities outside of those examined here.[71]

Conclusion

FSWs constitute a large, vulnerable, hard-to-reach population that could be amenable to mHealth interventions given their high mobile phone coverage and utilisation. FSWs are at considerable risk of unintended pregnancies, and could markedly benefit from interventions that increase uptake of contraception, with an emphasis on long-acting reversible technologies and dual method use. Similarly, the nutrition arm of the trial responds to the paucity of quality data on rates of malnutrition among sex workers and of effective interventions to improve their nutritional status and metabolic health.

A cluster-RCT with an equal-attention control and objective biological primary endpoints (unintended pregnancy and anaemia) is the most robust study design to test the effectiveness of the planned interventions. It is anticipated that the trial will contribute important evidence to mHealth initiatives among vulnerable populations and provide useful methodological insights into the use of reciprocal control groups within such trials.

Author declarations

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Author contributions

The following authors were investigators on the trial from the outset (Frances Ampt, Collins Mudogo, Peter Gichangi, Megan Lim, Matthew Chersich, Walter Jaoko, Marleen Temmerman, Marilyn Laini, Liz Comrie-Thomson, Mark Stoové, Paul A. Agius, Margaret Hellard, Kelly L'Engle, Stanley Luchters). Griffins Manguro more recently joined the trial site in Kenya, leading work in that site. The paper draws from the trial protocol, which was written collectively, under the leadership of the Principal Investigator Stanley Luchters. The final version of the paper was read and approved by all authors.

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Competing Interests

None declared

Ethics approvals

Monash University (MUHREC)

Kenyatta National Hospital Ethics and research committee.

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

Data presented in this paper are available from the corresponding author on request.

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Figure 1. Logic model for the sexual and reproductive health intervention (WHISPER)

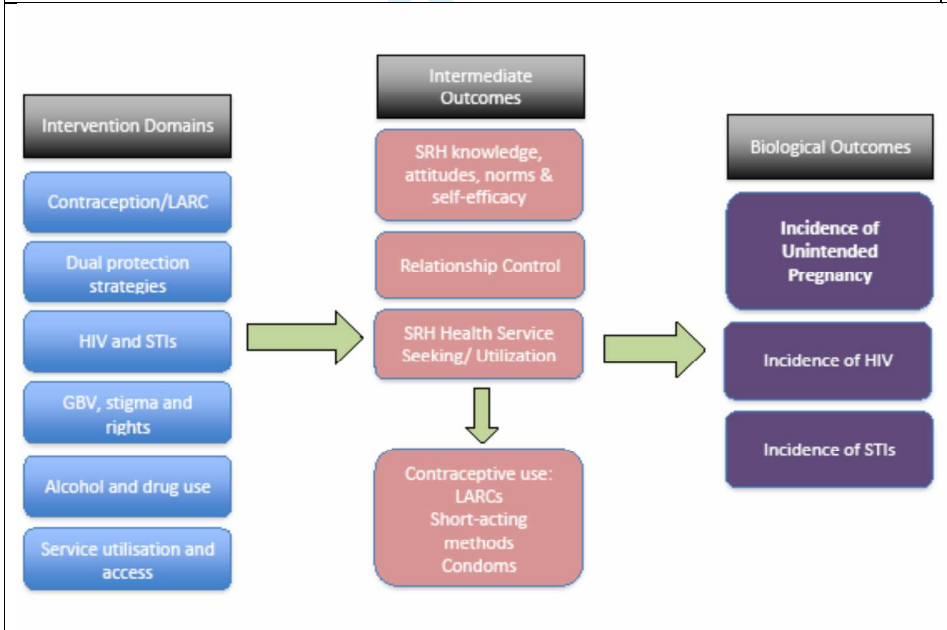
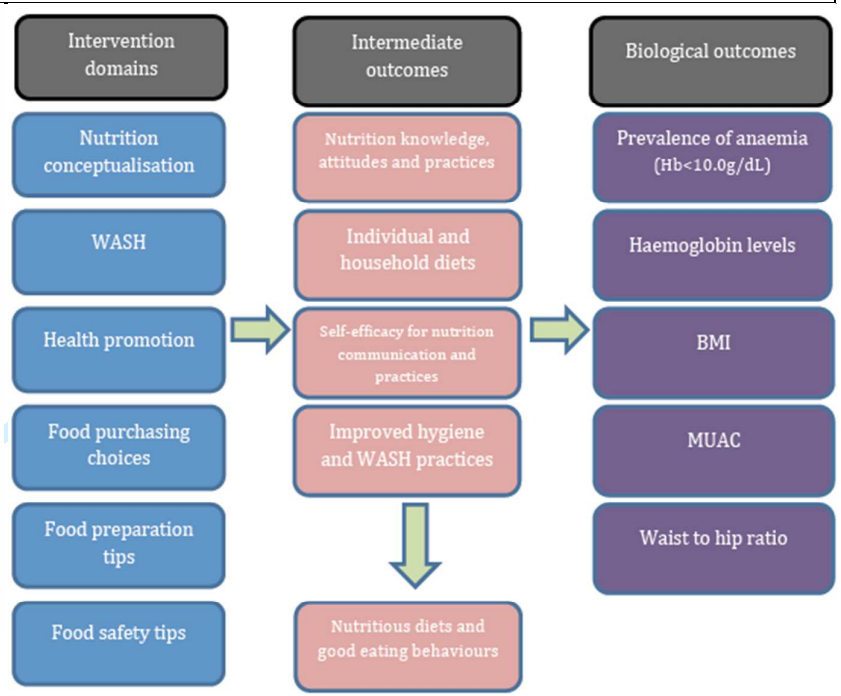


Figure 2. Logic model for the nutrition intervention (SHOUT)



Women's Health Intervention using SMS for Preventing Unintended Pregnancy (WHISPER)

or

SMS intervention to improve nutritional Heath OUTcomes (SHOUT)

A cluster Randomised Controlled Trial assessing mHealth interventions among female sex workers in Mombasa, Kenya

International Clinical Trials Registry number: ACTRN12616000852459

WHISPER or SHOUT study protocol, version 1.2, dated August 22nd, 2016

1 Executive summary

Female sex workers (FSWs) are at considerable risk of unintended pregnancies, which contribute substantially to maternal and perinatal morbidity and mortality, and socioeconomic vulnerability. Public health interventions that increase uptake of family planning methods among FSWs, including dual protection (use of condoms and another modern method of contraception), could markedly benefit this population. In addition, there is a growing acknowledgement of the potential importance of nutrition in the population, and the paucity of quality data on rates of malnutrition among sex workers and effective interventions to improve their nutritional status and metabolic health.

The WHISPER (Women's Health Intervention Using SMS to Prevent Pregnancy) or SHOUT (SMS Intervention to improve nutritional Health OUTcomes) study will assess the effectiveness of two mobile phone-based health promotion interventions to reduce the incidence of unintended pregnancy, and the prevalence of anaemia respectively, among female sex workers in Mombasa, Kenya. The study is a collaboration between the International Centre for Reproductive Health (ICRH) in Kenya and the Burnet Institute in Australia, along with collaborating investigators from other institutions. It is funded by the National Health and Medical Research Council of Australia.

In phase 1 of the study, mHealth text messages for both the sexual and reproductive health (WHISPER) and nutrition (SHOUT) interventions were developed and tested in formative research with female sex workers (ethics approval for phase 1 provided by KNH UoN ERC and Monash University).

This is the protocol for phase 2, which will consist of a 12-month cluster-randomised controlled trial to assess the effectiveness of the SMS-based interventions. One group will receive the SRH intervention and the other will receive the nutrition intervention, with each acting as the equal attention control group for the other. Eligible women will be recruited from sex work venues (clusters) by well-established peer outreach workers. FSWs will be randomised to the SRH or nutrition intervention, with assessments conducted at baseline, six, and 12 months follow-up. Data collection will include semi-structured face-to-face interviews as well as anthropometry and biological testing for pregnancy, HIV, syphilis and nutritional health parameters (e.g. haemoglobin). A validation study called Eyenaemia, which tests a novel technology for diagnosing anaemia, will be nested in the trial, with a separate consent process for interested participants.

In addition to the primary outcomes, a number of secondary outcomes will also be assessed. For WHISPER these include dual method and long-acting reversible contraceptive use, incidence of HIV, self-reported abortion and contraceptive knowledge score. For SHOUT, they include malnutrition by measured BMI, self-reported nutritious diet, and nutrition knowledge score.

As part of evaluating the feasibility and acceptability of the WHISPER intervention, qualitative interviews will be conducted at the conclusion of the study with a sample of

participants from the sexual and reproductive health arm, and their emotional partners. Interviews will explore positive and negative attributes of the SRH intervention, and explore in depth how it influenced the attitudes, behaviours and practices of female sex workers, and their relationship with their emotional partner(s).

If shown to be effective in this trial, mHealth interventions could be incorporated into broader SRH and/or nutrition strategies for FSWs in Africa and elsewhere, and have the potential to be scaled up for use with other women at a population level at low cost.

2 Acronyms and definitions

AIDS	Acquired Immunodeficiency Syndrome
Anaemia	Haemoglobin level below the normal range. Mild anaemia: haemoglobin of 10.0-11.9 g/dL (9.0-10.9 g/dL in pregnant women) Moderate anaemia: haemoglobin of 8.0-9.9 g/dL (9.0-10.9 g/dL in pregnant women) Severe anaemia: haemoglobin of 7.9 g/dL or below (6.9 g/dL or below in pregnant women)
BMI	Body mass index
FP	Family planning
FSW	Female sex worker
GBV	Gender based violence
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
ICRH	International Centre for Reproductive Health
LARC	Long-acting reversible contraception
MUAC	Mid upper-arm circumference
MCV	Mean Cell Volume
NCD	Non communicable disease
O/O	Overweight/Obesity
SRH	Sexual and reproductive Health
STI	Sexually transmitted infection

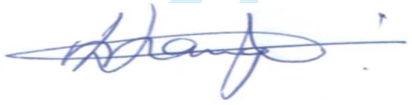
SMS	Short Message Service, or text messages
WASH	Water, sanitation and hygiene
WHO	World Health Organization

3 Investigators' signature page

"I have read this protocol and appendices and agree to conduct the trial as stipulated, and in compliance with all applicable regulations and guidelines."

Principal Investigator

Prof. **Peter Gichangi**, Principal Investigator, International Centre for Reproductive Health, Mombasa, Kenya



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Chief Investigators

Prof. **Walter Jaoko,** Chief Investigator, University of Nairobi, Kenya

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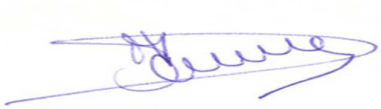
Prof. **Marleen Temmerman**, Chief Investigator, Aga Khan Foundation, Kenya



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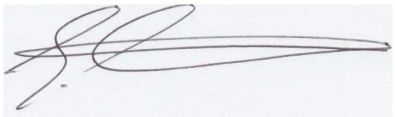
Associate Prof. **Stanley Luchters**, Chief Investigator, Burnet Institute, Australia



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Dr. **Megan Lim**, Chief Investigator, Burnet Institute, Australia

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Prof. **Margaret Hellard**, Chief Investigator, Burnet Institute, Australia

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Associate Prof. **Mark Stoové**, Chief Investigator, Burnet Institute, Australia

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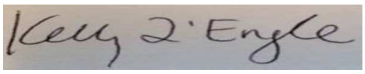
Associate Prof. **Kelly L'Engle**, Chief Investigator, University of San Francisco, USA



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Associate Prof. **Matthew Chersich**, Chief Investigator, University of the Witwatersrand, South Africa

23/8/2016…… ……

Signed and dated *dd/mm/yyyy*

Co- Investigators

Mr Collins Mudogo, co-investigator, ICRH, Kenya

23/8/2016…… ……

Signed and dated *dd/mm/yyyy*

Dr Frances Ampt, co-investigator, Burnet institute, Australia

23/8/2016…… ……

Signed and dated *dd/mm/yyyy*

Mr Paul Agius, Statistician and co-investigator, Burnet Institute, Australia

23/8/2016…… ……

Signed and dated *dd/mm/yyyy*

4 Contact details

International Centre for Reproductive Health (ICRH), Kenya	Peter Gichangi	e-mail: Peter@icrhk.org
	Collins Mukanya Mudogo	e-mail: CMudogo@icrhk.org
University of Nairobi, Kenya	Walter Jaoko	e-mail: WJaoko@KAVIUON.ORG
Aga Khan University, Kenya	Marleen Temmerman	e-mail: marleen.temmerman@ugent.be
Wits Reproductive Health and HIV Institute, University of the Witwatersrand, South Africa	Matthew Chersich	e-mail: mchersich@wrhi.ac.za
Burnet Institute, Australia	Stanley Luchters	e-mail: sluchters@burnet.edu.au
	Megan Lim	e-mail: lim@burnet.edu.au
	Mark Stoove	e-mail: stoove@burnet.edu.au
	Margaret Hellard	e-mail: hellard@burnet.edu.au
	Frances Ampt	e-mail: frances.ampt@burnet.edu.au
University of San Francisco, USA	Kelly L'Engle	e-mail: klengle@usfca.edu

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6 Research outline

Aim:	The overall aim is to improve the health and wellbeing of female sex workers in resource-constrained settings. This study assesses the effectiveness of two mobile phone delivered interventions and aims to: 1) improve the sexual and reproductive health of female sex workers (as compared to women receiving a nutrition intervention), and 2) improve the nutritional status of female sex workers (as compared to women receiving an SRH intervention).	
Study objectives	1 - SRH intervention	2 - Nutrition intervention
Primary objective:	To assess the effectiveness of a 12-month mobile phone-based sexual and reproductive health promotion intervention to reduce the incidence of unintended pregnancy among FSWs in Kenya.	To assess the effectiveness of a 12-month mobile phone-based nutritional health promotion intervention on nutritional status (particularly anaemia) among FSWs in Kenya.
Primary study endpoint:	Incidence of unintended pregnancy over 12 months of follow-up.	Nutritional status and prevalence of anaemia (Hb<12.0g/dL) at 12 months of follow-up.
Secondary Objectives:	i) to assess the feasibility and acceptability of the mobile phone delivered sexual and reproductive health intervention ii) to assess the effectiveness of the intervention at reducing HIV and syphilis incidence iii) to assess the effectiveness of the intervention at improving contraceptive knowledge (median knowledge score).	i) to assess the feasibility and acceptability of the mobile phone delivered nutrition intervention ii) to assess performance, feasibility and acceptability of a mobile phone administered application (Eyenaemia) for measuring anaemia (sub-study).
mHealth intervention description:	The intervention addresses knowledge of contraceptive options and their effectiveness and safety, and improvements in sexual and reproductive health self-efficacy, particularly through the promotion of long-acting reversible contraceptive methods and injectable contraception (non-user-dependent methods).	The nutritional health promotion intervention promotes positive knowledge, attitudes and practices regarding locally applicable actions, which could improve nutritional status of women of childbearing age.

mHealth intervention delivery	Mobile phone delivered health promotion intervention consisting of: * health messages sent through a series of SMS; * theory-guided role model stories available as phone messages promoting positive norms and attitudes, and increased self-efficacy for healthier behaviour; * on-demand system for more detailed SMS delivered information.
Design:	Two-arm cluster randomised controlled trial with women recruited from 86 sex work venues; Qualitative inquiries consisting of in-depth interviews will be conducted to assess secondary objectives with regards to feasibility and acceptability of the intervention.
Location	Mombasa County, Coast Region, Kenya.
Study population	Women in the study areas, aged 16 years or older, who self-report receiving money in exchange for sex in the last six months, not currently pregnant, and not planning a pregnancy in the next 12 months.
Study size	860 female sex workers (430 women per arm) enrolled from 86 female sex worker venues. In total an estimated 40 in-depth interviews will be conducted.
Study duration	6-month enrolment period with 12-months follow-up.

7 Background

7.1 Unmet need for family planning among women

Contraception has profound benefits for women and society, including reduced maternal and infant mortality and morbidity, empowerment of women to make informed choices about fertility, economic advancement, and a reduction in the number of children infected with HIV (Feucht, Meyer et al. 2014;Michalow, Chola et al. 2015). In recent decades, contraceptive use has risen markedly worldwide, though at a much slower pace in sub-Saharan Africa than elsewhere (Cleland, Harbison et al. 2014). About a quarter of women in sub-Saharan Africa currently use modern contraceptive methods, with levels highest in southern Africa (United Nations (UN) Department of Economic and Social Affairs Population Division 2013; Darroch and Singh 2013). In South Africa, for example, estimates of the proportion of women of reproductive age who are protected against unplanned pregnancies using modern contraceptive methods have increased steadily from 26.3% in 2002/03 to 37.3% in 2013/14 (Massyn, Day et al. 2014). However, the continued rise in the number of terminations of pregnancy in the country and elsewhere, among all age groups, suggests that substantial deficiencies remain in access to family planning services (Massyn, Day et al. 2014).

Increasing the range of contraception choices available is a key component of ensuring access for women, their partners and for couples, to the most effective method they wish to use. Particular emphasis has been placed on raising access to long-acting reversible contraception (LARC) methods, including intrauterine devices and subdermal implants. These are highly effective, and markedly diminish the need for user adherence and contact with health workers. Many health providers, however, still unfamiliar with these methods (Gutin, Mlobeli et al. 2011; Morse, Chipato et al. 2013; Blanchard, Chipato et al. 2014). Throughout sub-Saharan Africa, the injectable progestins depot-medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN) are the most popular modern contraceptive methods (Darroch and Singh 2013). About 5.8 million doses of DMPA are administered annually (Massyn, Day et al. 2014). Its use has continued to rise over time in Southern and Eastern Africa (Ross and Agwanda 2012). By contrast, in most high-income countries, use of injectable contraceptives is rare, aside from in marginalised groups, such as poor, non-white or Aboriginal women (Tait 2000; Smith 2003; Metoyer 2009; Volscho 2011). The popularity of injectables in sub-Saharan Africa is ascribed to its convenience for providers and women, cost effectiveness, and high acceptability among women and health providers (Michalow, Chola et al. 2015). Method discontinuation and contraceptive failure are, however, frequent with this method (Baumgartner, Morroni et al. 2007; Smit and Beksinska 2013).

MHealth interventions for SRH often face a challenge in providing uncontroversial information on “safe” topics, “topics about mothers and feel-good sensations”, and covering

more controversial or even taboo topics (Waldman and Stevens 2015). As an overarching principle, it is important to tackle the issues that constitute barriers to care, even those that are more complex and difficult to handle. Such topics include health care workers' abuse and disrespect, as well as how women might deal with an unintended pregnancy and its consequences (Waldman and Stevens 2015). It is thus important to measure factors influencing the supply of family planning services, not just demand for them.

7.2 Sexual and reproductive health of female sex workers

Reducing unmet need for contraception could prevent 52 million unintended pregnancies, 70,000 maternal deaths, and 500,000 newborn deaths annually (Singh, Darroch et al. 2014). Unmet need is a particular concern for female sex workers (FSWs), with approximately one quarter of FSWs in Kenya experiencing an unintended pregnancy each year (Chersich, Bosire et al. 2014). Given the very high rates of HIV in this population in sub-Saharan Africa (Scorgie, Chersich et al. 2012), sexually transmitted infection (STI) prevention has been the primary aim of health promotion. This vertical approach, however, has largely overlooked FSWs' broader reproductive health needs.

With nearly one in 20 women in sub-Saharan Africa engaged in sex work (Vandepitte, Lyerla et al. 2006), FSWs constitute a large, vulnerable, hard-to-reach population. Mobile phones offer a promising means of accessing this population given their high penetration in Kenya and among FSWs in particular (ITU 2016), (Vahdat, L'Engle et al. 2013). Health promotion delivered through mobile phones has the potential to reach a large number of at-risk women at low cost, and address known barriers to contraceptive use including lack of knowledge and misconceptions (Sutherland, Alaii et al. 2011). RCTs among young people in Australia demonstrate that mHealth interventions can increase SRH knowledge and service uptake (Gold, Aitken et al. 2011; Lim, Hocking et al. 2012). No trials have yet been published on the impacts of mHealth on SRH among sex workers or in low income countries.

7.3 Malnutrition among adult women

Investing in nutrition is as much an issue of health, of care, and of food sovereignty, as it is of human rights, of economic welfare, and of social protection. Nutrition should be central to all renewed commitments to realise the Sustainable Development Goals (SDGs)(United Nations Development Programme 2015).

Worsening food insecurity in urban poor settings in SSA is one of the leading direct and indirect causes of morbidity and mortality among women and children. The nature, extent and duration of coping strategies to food insecurity in urban settings by women, determine the magnitude and severity of their suffering and that of their children (Kimani-Murage, Schofield et al. 2014). Studies in many countries including Kenya, Ethiopia, Swaziland, Brazil, and Nigeria indicate that hunger is a key factor pushing women into sex work (Hampanda

2013; Njue, Voeten et al. 2011; Fielding-Miler, Minisi et al. 2014; Oyefara 2007; Moret 2014). Food insecurity has been linked to not only lead women into sex work but also increase their chances of engaging in risky sexual behaviours for survival (Tsai, Hung et al. 2012). Micronutrients deficiency is known to have staggering consequences for human health and well-being as well as hampering economic productivity. In women of reproductive ages, micronutrients deficiency lead to increased pregnancy complications and maternal mortality (Children's Investment Fund Foundation 2013; Stoltzfus and Dreyfuss n.d.; World Health Organization & Food and Agricultural Organization of the United Nations n.d.). On the other hand, overweight and obesity causes poor health, negatively affects quality of life and shortens the quantity of life. Uniquely in women, obesity causes conditions such as osteoarthritis, birth defects, breast and endometrial cancers, cardiovascular and gall bladder diseases, infertility, gynaecological complications, urinary stress incontinence, stigma and discrimination (Mbochi, Kuria et al. 2012).

Food security is based on four main processes, including food availability, food access, food utilisation, and food stability (Gross, Schoeneberger et al. 2000; Fanzo 2012). The 2011 National Food and Nutrition Policy in Kenya highlights four broad objectives including; to achieve good nutrition for optimum health of all Kenyans, to increase the quantity and quality of food available, accessible and affordable to all Kenyans, to protect vulnerable populations using innovative and cost-effective safety nets linked to long term development (Government of Kenya Agricultural Sector Coordination Unit 2011). In essence, it is important to conceptualise nutrition beyond just the aspects of food intake, absorption and metabolism, hence consider the balance between what is eaten vis-a-vis what the body requires (African Union 2005).

Using the concept of hidden hunger, which is associated with micronutrient deficiencies, the Food and Agricultural Organization (FAO) estimates that 850 million people across the world are hungry. FAO states that malnutrition is purported to affect up to a half of the world's population (Henson and Humphrey 2013). Iron deficiency is the most prevalent single nutrient deficiency affecting an estimated 2 billion people worldwide. Iron deficiency and anaemia are known to be most prevalent in developing countries. Although Iron deficiency can occur at any stage in a life cycle (World Health Organization 2001), the most vulnerable groups include women and children. Globally 469 million women of reproductive age are anaemic with at least 50% of this resulting from dietary iron deficiency (Oldewage-Theron et al. 2014). In South Africa, studies have reported iron deficiency in 7-29% of pregnant women, 57% in pregnant teenage girls, 21% in infants and 26% in non-pregnant teenage girls (Aderibigbe 2011). In many SSA countries, including Kenya, under nutrition is associated with wide spread micronutrient deficiencies (Rohner et al. 2016; Amuyunzu-Nyamongo 2011; Fanzo 2012; Claxton n.d.; Dixon, Omwenga et al. 2007; Kimani-Murage et al. 2015).

Women and children within settings of high vulnerability to food security are more likely to rely on pre-prepared and street based high energy dense foods which predispose them to

obesity. Moreover access to low quality food, limited in dietary diversity may lead to obesity, conditions typical of the urban poor women and children in many Kenya (Kimani-Murage, Muthuri et al. 2015).

While Kenya's overall budget has increased over time, budgetary allocation for food security and agriculture has remained lower than the minimum recommended 10% by the African Union meeting in Maputo in 2003 (FAO 2015). For example in the 2015/16 budget, worth 2 trillion, food and agriculture were only allocated 43.3 billion translating to about 4.3%. This is despite the rapidly rising food inflation in the country (Republic of Kenya Parliamentary Service Commission & Parliamentary Budget Office 2015). In finding solutions to the already overburdened resource constraint healthcare systems in SSA, it is important to appreciate that long-term health outcomes are shaped by factors largely outside of the health system such as lifestyle, diet and nutritional levels and education (National Planning Commission 2012).

7.3.1 Dietary diversity and intake

A variety of foods in the diet is needed to ensure an adequate intake of essential nutrients. Dietary diversity can be used as a proxy measure of the nutritional quality of a population's diet, as well as an indicator of the access dimension of household food security (Kennedy, Pedro et al. 2009). Populations consuming a diet of low dietary diversity are nutritionally vulnerable (Kennedy, Pedro et al. 2009).

In measures of diversity, participants are asked to recall all foods and drinks consumed the previous day. These food items were then allocated to specific food groups. A dietary diversity score (DDS) is calculated by summing the number of food groups from which food had been consumed; the nine food groups were cereals, roots and tubers; vitamin A-rich vegetables and fruit; vegetables other than vitamin A is rich; fruit other than vitamin A-rich fruit; meat, poultry, and fish; eggs; legumes; dairy products; and foods made with fats or oils. Each food group was counted only once. A DDS below four is considered to be low and to be associated with dietary inadequacies (Steyn 2006) .

No single food contains all required nutrients for optimal health. Consequently, the more food groups included in a daily diet, the greater the likelihood of meeting nutrient requirements (Kennedy, Pedro 2009) . Monotonous diets, based mainly on starches such as maize, rice and bread, have been closely associated with food insecurity. Dietary diversity is an outcome measure of food security at the individual or household level (Kennedy 2009) . Apart from reflecting on food security, low dietary diversity has also been associated with low weight and stunted growth (Rah 2010) #30} , cardiovascular risk (Azadbakht 2006)dyslipidaemia (Li, Wedick et al. 2011), as well as a risk factor for the metabolic syndrome (Azadbakht 2006).

The increase in the prevalence of chronic diseases in the developing world is largely attributed to changes in lifestyle associated with globalisation and urbanisation (WHO 2003). Studies from populations throughout the world have demonstrated a strong association of obesity with chronic NCDs, especially type 2 diabetes, and cardiovascular diseases (Popkin 2002). A high energy intake is one of the main risk factors for obesity in both children and adults. This, together with a high total fat intake, high saturated fat intake, high refined carbohydrate and added sugar intake, low fibre intake and low intake of fruits and vegetables, has been classified as a typical 'western diet' which contributes to the development of chronic diseases. This process has been described by many as the nutrition transition (Popkin 2002).

The field of anthropometry encompasses a variety of human body measurements, such as weight, height, and size, including skinfold thicknesses, and circumferences. In adults, body measurement data are used to evaluate health and dietary status, disease risk, and body composition changes that occur over the adult lifespan. Anthropometry provides the single most portable, universally applicable, inexpensive and non-invasive technique for assessing the size, proportions, and composition of the human body. It reflects both health and nutritional status and predicts performance, health and survival. As such, it is a valuable tool for guiding public health policy and clinical decisions (WHO1995). The body mass index (BMI) is a measure of nutritional status that combines weight with height data. It provides an acceptable approximation for assessment of total body fat and is a fairly reliable indicator of body fat for most adults, with athletes and the elderly being two exceptions. The BMI has been considered to be the most appropriate and simple indicator by which weight-for-height can be related to health outcomes. It is widely acknowledged that the risk of illness increases with modest increases in weight, starting from a BMI of about 21 kg/m2 (Rigby 2006). Alternative measures that reflect abdominal adiposity, such as waist circumference, waist–hip ratio and waist–height ratio, have been suggested as being superior to BMI in predicting cardiovascular disease (CVD) risk (WHO 2011). This is based largely on the rationale that increased visceral adipose tissue is associated with a range of metabolic abnormalities, including decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles, which are risk factors for type 2 diabetes and cardiovascular disease (CVD). Waist–hip ratio (the waist circumference divided by the hip circumference) can be measured more precisely than skin folds, and it provides an index of both subcutaneous and intra-abdominal adipose tissue.

7.3.2 Iron deficiency

Because anaemia is the most common indicator used to screen for iron deficiency, the terms anaemia, iron deficiency, and iron deficiency anaemia are often used interchangeably. According to WHO, iron deficiency is the most common nutritional disorder in the world. It affects at least half of all pregnant women and young children in developing countries. Iron deficiency often results from a lack of bioavailable iron in the diet, but also can occur during a period of rapid growth (pregnancy and infancy), when the body needs more iron. Another

common cause is increased blood loss, such as gastrointestinal bleeding due to hookworm or urinary blood loss due to schistosomiasis.

Multiple causes of anaemia can coexist in an individual or populations and contribute to its severity; however, the most common cause of anaemia is iron deficiency. Among adults, anaemia is a serious risk to mothers in childbirth: every day some 140 women die in childbirth because of severe anaemia. Although some functional consequences may be observed in individuals who have iron deficiency without anaemia, cognitive impairment, decreased physical capacity and reduced immunity are commonly associated with iron deficiency anaemia. In severe iron deficiency anaemia, capacity to maintain body temperature may also be reduced. Severe anaemia is also life threatening. Because anaemia can contribute to maternal mortality, infant morbidity, infant mortality, intrauterine growth retardation and low birth weight, WHO recommends screening of all pregnant women for anaemia. Iron deficiency has also been associated with overweight and obesity (Bougle and Brouard 2013; Oldewage-Theron, Egal et al. 2014; Aderibigbe 2011; Bouglé & Torheim, Elaine et al. 2010)

Clinical signs and biochemical test for anaemia

Using clinical pallor of the nails or eyes (inferior conjunctiva) to diagnose anaemia on a population basis should be avoided because these clinical signs are very subjective and not precise. Haemoglobinometers, such as the HemoCue is a more reliable and easy method is to test the haemoglobin concentration in the blood (World Food Programme 2005). Compared to the HemoCue method, an objective method, the haemoglobin colour scale and the Sahli method have low accuracy (World Food Programme 2005; M'Baya, Mbingwani et al. 2014). They are not recommended in research or field surveys of nutrition (World Food Programme 2005).

The World Health Organization defines anaemia as Hb< 12.0g/dL (<11g/dL for pregnant women), and severe anaemia as Hb< 8.0g/dL (<7g/dL for pregnant women) (WHO 2015). In clinical practice in Kenya, anaemia is generally defined as Hb< 10.0g/dL (Republic of Kenya 2009); however this study will be adopting the World Health Organization definition.

7.4 Nutritional health needs in Kenya

The National Food and Nutrition Security Policy of 2011 states that all Kenyans should at all times have access to safe food of sufficient quantity and quality to satisfy their nutritional needs for optimal health. Although research in many countries show that food insecurity and poor diets have been associated with entry into sex work and relatively high propensity of engaging in unprotected sex (Moret 2014; Neal, Schrader et al. 2014;Tsai, Hung et al. 2012),we could not locate any data on nutritional assessment of FSWs in Kenya, and thus provide a background on nutrition in Kenya as a whole. Clearly, this study will provide much useful information on nutrition among the FSW population in the country.

In the Kenya 2014 Demographic and Health Survey, the majority of households (89 percent) had acceptable food consumption scores (KDHS 2014). The food consumption score, derived from the household consumption history questions, is a composite calculation including dietary diversity (the number of food groups consumed by a household over a seven-day period), food frequency (the number of days a particular food group is consumed), and the relative nutritional importance of different food groups. The score is intended to describe short-term food security at the time of data collection. Food consumption scores are divided into poor, borderline, and acceptable food consumption groups. Two percent of households had poor food consumption scores and 10 percent had borderline scores.

Kenya's nutritional profile indicates that iron and Vitamin A deficiencies are the most prevalent in the country. For example in 1999, just over half (55%) of pregnant women and just below one half, 47.9% of non-pregnant women suffered from iron deficiency anaemia. In 2011, 36% of pregnant women were estimated to have blood haemoglobin concentration of less than 11g/dl while 25 % of non-pregnant women were estimated to have blood haemoglobin concentration of less than 12g/dl (WHO 2015). Approximately 40% of women experience vitamin A deficiency. 17% of pregnant women in Kenya are Vitamin A deficient with about 52% of mothers being zinc deficient. Although there is a dearth of information, iodine deficiency disorders are still prevalent in Kenya (Muthoni 2014).

Overweight and Obesity (O/O) are modifiable risk factors for the development of non-communicable diseases (NCDs). With the current increasing rates in O/O of about 5% per year across SSA, there are high predictions of accompanying increase in NCDs and diabetes mellitus 2. Across SSA, the prevalence of overweight/obesity appear to be most visible among populations in urban settings. Factors such as dependence on ready and fast foods, reduced physical activity, imbalanced diet, and poverty, seem to predispose urban poor populations to O/O more than their rural counterparts(Kimani-Murage 2013; Mohiddin, Phelps et al. 2012). A study in the poor urban slums of Nairobi confirmed the existence of the double burden of malnutrition in such settings in Kenya. In that study 7.5% mothers were underweight while 32% were obese. Interestingly, a large proportion, 43% and 37% of the overweight and obese mothers respectively had stunted children (Kimani-Murage, Muthuri et al. 2015). O/O are usually more prevalent in women specifically in the 25 to 40 age range. This is mainly attributable to the retention of gestational weight gain and also the outcome of numerous lifestyle factors such poor diets, inactive lifestyles, urbanisation and adoption of diets that veer away from traditional menus (Mbochi, Kuria et al. 2012).

Female sex workers in Mombasa are vulnerable to poor nutritional status due to many historical, social, economic and environmental factors. The SHOUT study will elicit reflections on the need to think about nutrition among FSW. The SHOUT study has been designed to promote knowledge and information, that can holistically improve nutrition status among female sex workers by influencing their attitudes and practices towards better food purchasing practices, better methods of food storage, better methods of food preparation, better diets, better eating habits and improved hygiene.

7.5 Potential of mHealth to address barriers and promote healthy behaviours

Mobile technology interventions hold enormous promise for health promotion. One of the most popular communication technologies is short message service (SMS), also known as text messaging. SMS has many advantages over other modes of communication. SMS is transmitted between mobile phones, so is not dependent on fixed lines or non-portable equipment and can be received anywhere. It is fast, with transmitted messages being received almost instantaneously. It is convenient; a message can be stored in the phone until the recipient is ready to read it and when saved in the phone, the recipient can refer to it at any time. It can be anonymous; the sender and recipient do not have to reveal anything about themselves other than their mobile number, and recipients can choose to ignore or respond to a message after reading its content. It is highly cost-effective; sending a text message costs less than a fixed-line local phone call and messages can be sent to many recipients at once. Direct evidence for the effectiveness of SMS health promotion interventions is rapidly evolving.

Three recent systematic reviews have shown that SMS interventions influence behaviour change and can successfully promote health seeking, (Fjeldsoe, Marshall et al. 2009, Cole-Lewis and Kershaw 2010; Free, Phillips et al. 2013) including for sexual health and diet. A series of randomised-controlled trials in Australia that demonstrated improvements in sexual health outcomes following an SMS intervention (Gold, Aitken et al. 2011; Gold, **Lim** et al. 2011; **Lim**, Hocking et al. 2012). Importantly, this research showed that, in response to regular SMS and email messages, young women (in comparison to men) were particularly sensitive to improved their health seeking behaviour including being significantly more likely than controls to have an STI test or talk to their doctor about sexual health (**Lim**, Hocking et al. 2012). Trials in high income countries have also demonstrated the efficacy of SMS for changing diet behaviours (Nguyen, Kornman et al. 2011).

In developing countries, mobile phones are an increasingly important means of communication with broader reach and penetration than any other forms such as fixed line phones, radio, television or the internet (International Telecommunication Union 2014). Worldwide, around 80% of people living in developing countries own a mobile phone, making SMS a feasible and scalable method of health promotion in resource-poor settings. Kenya is a leader among developing economies in mobile technology for development (International Telecommunication Union 2014).

Formative qualitative research in Mombasa showed that mobile phones are essential and ubiquitous items for FSW. Most reported frequent text messaging, with 20-100 messages per day used to communicate with clients, friends and family, and for generating business. FSW reported not sharing phones with others and considered them as among their most valuable possessions; most FSW protected their phones because they kept their life savings

on them with mPesa (a mobile finance system in Kenya). Importantly, Mombasa-based FSW indicated interest in receiving health messages on their phones, even multiple times per day, as long as they did not have to pay for them. Research with FSW in Dar es Salaam, found that 94% of women indicated they 'would definitely pay attention to health texts' (**L'Engle**, Vahdat et al. 2013).

8 Study rationale

FSWs are at considerable risk of unintended pregnancies, which contribute substantially to maternal and perinatal morbidity and mortality, and socioeconomic vulnerability. Public health interventions that increase uptake of family planning methods among FSWs, with an emphasis on dual method use, could markedly benefit this population. FSWs constitute a large, vulnerable, hard-to-reach population that could be amenable to mHealth interventions given their high mobile phone coverage. There is promising evidence that health promotion messages using mobile phones are effective and offer a feasible means of: improving FSW knowledge of contraceptive options; modifying attitudes towards contraception; increasing reproductive health self-efficacy; raising uptake and utilisation of family planning methods; and consequently reducing unintended pregnancy.

Despite these potential gains and the proliferation of mHealth activities, there remains a lack of rigorous academic research in this emerging field, particularly which evaluates sexual and reproductive health promotion initiatives in resource-constrained settings(Lim, Hocking et al. 2008, Gold, Lim et al. 2011; Free, Phillips et al. 2013). A recent review of mHealth interventions found that although use of these technologies is increasing rapidly, research is failing to keep up (Free, Phillips et al. 2013).

The WHISPER study has been developed in response to the substantial SRH needs of FSWs in Kenya, the potential gains offered by increasing demand for family planning among FSWs through mHealth, and the research gaps in this field. In addition, the nutrition (comparison) arm of the trial has arisen out of a growing acknowledgement of the need to improve nutrition in this population, and the paucity of quality data on rates of malnutrition among sex workers and effective interventions to improve their nutritional status and metabolic health.

The WHISPER mobile messages have been developed in a systematic and participatory manner, to ensure that the intervention is grounded in evidence and health promotion theory, relevant and acceptable to the study population, and culturally appropriate. Evidence shows that theory-driven, interactive communication interventions that follow best practices in design and implementation can change attitudes and behaviours (Noar, Palmgreen et al.). A randomised controlled trial with an equal-attention control and objective biological primary outcome (unintended pregnancy) is the most robust study design to test the effectiveness of this intervention.

Development of the messages and role model stories for the SHOUT intervention was systematic and involved intensive and extensive formative research with the female sex workers population. Through a total of 10 workshops, female sex workers were involved in identifying important nutrition issues that affect them, developing of the messages and role model stories, reviewing and refining of the messages and role model stories, and generally in providing suggestions on the intervention architecture. This was in an effort to develop a relevant, acceptable and culturally appropriate intervention that is theory based. Key theories, models and processes of nutrition education underpin the importance for programs to improve knowledge, change attitudes and practices, with the understanding that behaviour change is a process and not an event, among individuals and communities to be able to promote sustainable positive behaviour changes (California WIC Program 2002).

If shown to be effective in this trial, mHealth could be incorporated into broader SRH and/or nutrition strategies for FSWs in Africa and elsewhere, and has the potential to be scaled up for use with other women at a population level.

9 Aims and study objectives

9.1 Aims

The aim of the study is to improve the health and wellbeing of female sex workers in resource constrained settings.

More specifically, this study aims to:

i) improve the sexual and reproductive health of female sex workers (as compared to women receiving a nutrition intervention), and

ii) improve the nutritional status of female sex workers (as compared to women receiving an SRH intervention).

9.2 Objectives 1: Sexual and reproductive health intervention

9.2.1 Primary SRH objective

The primary objective of the SRH intervention is to assess the effectiveness of a 12-month mobile phone-based sexual and reproductive health promotion intervention in reducing the incidence of unintended pregnancy among FSWs in Kenya.

Primary SRH endpoint (relating to primary SRH objective)

1. Incidence of unintended pregnancy among study participants over 12 months of follow-up.

   An unintended pregnancy is defined as one that is mistimed, unplanned, or unwanted at the time of conception. Women will be asked about their pregnancy intentions for the next 6 months at their baseline, and 6 and 12 month visits. A psychometrically-validated 6-item questionnaire (London Measure of Unintended Pregnancy) is used to score pregnancy intention in cases of pregnancy occurring during study follow-up. (Barrett, Smith et al. 2004) Pregnancy will be defined as either a self-reported pregnancy (confirmation not required) or as a result of urine pregnancy screening which is planned for at the 6 and 12 month visits, or at unscheduled study visits should these occur.

Secondary SRH endpoints (relating to primary SRH objective)

2. Proportion of female sex workers reporting the use of modern contraceptive methods ***and*** condoms consistently (dual protection) in past month with all partner types;
3. Proportion of female sex workers reporting the use of long-acting reversible contraceptive methods or injectable contraceptives at month 6 and month 12;
4. Incidence of self-reported abortion among study participants over 12 months of follow-up.

9.2.2 Secondary SRH objectives

The secondary objectives of the SRH intervention are:

i) To assess the effectiveness of the SRH intervention at reducing HIV/STI incidence over 12 months of follow-up among FSW in Kenya (HIV and syphilis measured at baseline, 6 months and 12 months)

ii) To assess the effectiveness of the SRH intervention at improving contraceptive knowledge (median knowledge score) after 6 and 12 months

iii) To assess the feasibility and acceptability of the SRH mHealth intervention.

9.3 Objectives 2: Nutrition intervention

9.3.1 Primary nutrition objective

The primary objective of the nutrition intervention is:

To assess the effectiveness of a 12-month mobile phone-based nutritional health promotion intervention on nutritional status among FSWs in Kenya

Primary nutrition endpoints (relating to primary nutrition objective)

1. Prevalence of anaemia (haemoglobin <12.0 g/dL, or <11g/dL if pregnant) among study participants at month 12.

   Anaemia will be assessed using a certified laboratory-based haematology machine. Assessment will be done at the 12-month visit.

Secondary nutrition endpoints (relating to primary nutrition objective)

2. Mean haemoglobin levels (units g/dL) among participants at month 12;
3. Proportion of female sex workers with malnutrition, either underweight (BMI < 18.5kg/m^2) or overweight (BMI ≥25 kg/m2)
4. Proportion reporting nutritious diet and good eating behaviour at month 6 and month 12.
5. Median score in nutrition knowledge among study participants at month 6 and month 12.

9.3.2 Secondary nutrition objectives

i) To assess the feasibility and acceptability of the nutrition mHealth intervention;

ii) To assess performance, feasibility and acceptability of a mobile phone administered application for measuring anaemia (sub-study).

10 Study design and methods

10.1 Study setting

The study will be conducted in two areas of Mombasa, a major economic centre in Kenya and East Africa, with busy port, rail and industrial enterprises. The International Centre for Reproductive Health (ICRH; a WHO Collaborating Centre for Reproductive Health in Mombasa) has a strong research track record including prospective intervention studies with FSWs (Thomsen, Ombidi et al. 2006; Luchters, Chersich et al. 2007; Pack, **L'Engle** et al. 2013; Bengtson, **L'Engle** et al. 2014 Accepted) and numerous non-intervention designs spanning almost 15 years(**Chersich**, **Luchters** et al. 2007; **Luchters**, **Chersich** et al. 2008; Luchters, Richter et al. 2013). ICRH in collaboration with the National AIDS and STI Control Programme (NASCOP) in Kenya did a two-stage geographic mapping and enumeration exercise of FSWs in 2010, and estimated that 9,288 (range 6,917-11,660) FSW operate from 744 venues across four Mombasa areas(National AIDS & STI Control Programme (NASCOP) and National AIDS Council (NAC) 2012). We will recruit FSW from two of these areas: Changamwe (where 1,223 FSWs work from 248 venues) and Kisauni (where 3,617 FSWs work from 263 venues) (National AIDS & STI Control Programme (NASCOP) and National AIDS Council (NAC) 2012). Sex work venues here include nightclubs, bars, hotels, private brothels, small businesses, street sites/corners.

10.2 Study design

This is a two-arm cluster randomised controlled trial to assess the effectiveness of two mHealth interventions (SRH and nutrition). Eligible women will be recruited from sex work venues (the clusters identified in the mapping exercise) by well-established peer outreach workers and randomised to receive either a 12-month sexual and reproductive health intervention or a 12-month nutritional health intervention via mobile phone (see intervention descriptions below). Effectiveness assessment will be done for each of the interventions with the other as the control group. As each intervention addresses a unique set of specific issues, and the delivery of the intervention is the same, they will each form an appropriate control group.

In addition, qualitative inquiries consisting of in-depth interviews will be conducted in the SRH study arm to further assess secondary objectives with regards to feasibility and acceptability of the intervention. Qualitative methods will explore both positive and negative attributes of the SRH intervention, and explore in depth how the intervention influenced the attitudes, behaviours and practices of female sex workers relating to sexual risk behaviour, family planning and FP service access. Moreover, we will explore how this influenced the relationship with their emotional (non-paying) partner(s). Women in the nutrition arm will not be included in the qualitative interviews. More detail about the qualitative inquiry is provided in Section 15.

10.3 Study population

FSW will be recruited from approximately 86 sex work venues (our clusters). We will sample each venue with a probability proportional to FSW population size at the venue, using a sampling frame based on the 2012 and/or 2014 mapping of venues and population enumeration (capture-recapture) previously conducted by our team (National AIDS & STI Control Programme (NASCOP) and National AIDS Council (NAC) 2012). Peer outreach workers familiar with the respective areas are responsible for inviting women to participate in the study. Women will be consecutively recruited from selected sex work venues. The study will be promoted at these venues and through word of mouth.

10.3.1 Inclusion criteria

To be eligible for participation in the study, the participants will have to meet the following criteria:

i) female gender
ii) be aged between 16 and 34 years of age (16 is the legal age of consent for research participation);
iii) self-report to have engaged in paid sex work at the recruitment hotspot in the last six months;
iv) have a personal mobile phone with Safaricom or Airtel subscription, and be willing to provide the number to the researchers, on which they can receive the mHealth intervention messages;
v) self-report to be 'SMS literate'
vi) not currently be pregnant or planning pregnancy within 12 months;
vii) reside, and plan to continue to reside, within the site-specific catchment area for the next 12 months, and be willing to return for follow-up at 6 months and 12 months; and
viii) be willing to provide reliable contact information (e.g. home address) to be contacted by a member of the research team in the community to remind them to re-attend follow-up visits; or be traced should these visits not be attended;
ix) be able and willing to give written informed consent for enrolment in the study.

10.3.2 Exclusion criteria

i) planning to travel or relocate from the study areas;
ii) participating in another mHealth intervention study; and
iii) having a medical or non-medical issue incapacitating participation in the research, as decided by the local Principal Investigator.

11 Description of the intervention

Both the SRH intervention and the nutrition intervention consist of SMS (text) messages sent to participants two to three times per week for 12 months. This includes the following components:

- Stand-alone 'push' texts covering the main content domains, providing simple information and strategies to prompt action;
- 'Role model stories' about FSWs modelling healthy social norms and sent in 4-5 instalments in one month (alternating months with stand-alone messages);
- 'Pull' on-demand menu that can be accessed by participants texting into the system to obtain more information on certain topics and local services.

The intervention will be delivered by VOTO mobile (https://www.votomobile.org/). This is an online mobile platform, which allows automated SMS and calls to be sent to many subscribers simultaneously, and pull content to be accessed via purchased shortcodes for specific mobile network providers (Safaricom and Airtel in this case). All messages will be loaded onto the system in pre-determined order and sent automatically to participants at the scheduled time (calculated from each cluster's start date). Participants will be able to text assigned codes at any time during the study to access the pull content, with SMS costs incurred by the study (no charge for participants). Participants will be grouped on the system by cluster, with nutrition and SRH content assigned to the corresponding group, so that those in the nutrition arm will not directly access SRH content and vice versa.

Based on findings from our formative research, the following table provides additional detail about the estimated number, length and timing of messages:

Message type	**Estimated number of messages**	**Length**	**Timing**[1]
Stand-alone push messages	77	Up to 160 characters (1 SMS 'screen'[2])	3 per week (sent Monday, Wednesday and Saturday mornings) during months 1, 3, 5, 7, 9, 11, 13[3]
Push interview reminders and WHISPER information	6	160 – 480 characters (2-3 screens)	
Role model stories	26 (covering 6 stories)	160 – 640 characters (2-4 screens) per message	2 per week (sent Monday and Friday mornings) during months 2, 4, 6, 8, 10, 12
'Alerts': push messages linking participants to the pull system	16	Up to 160 characters (1 screen)	

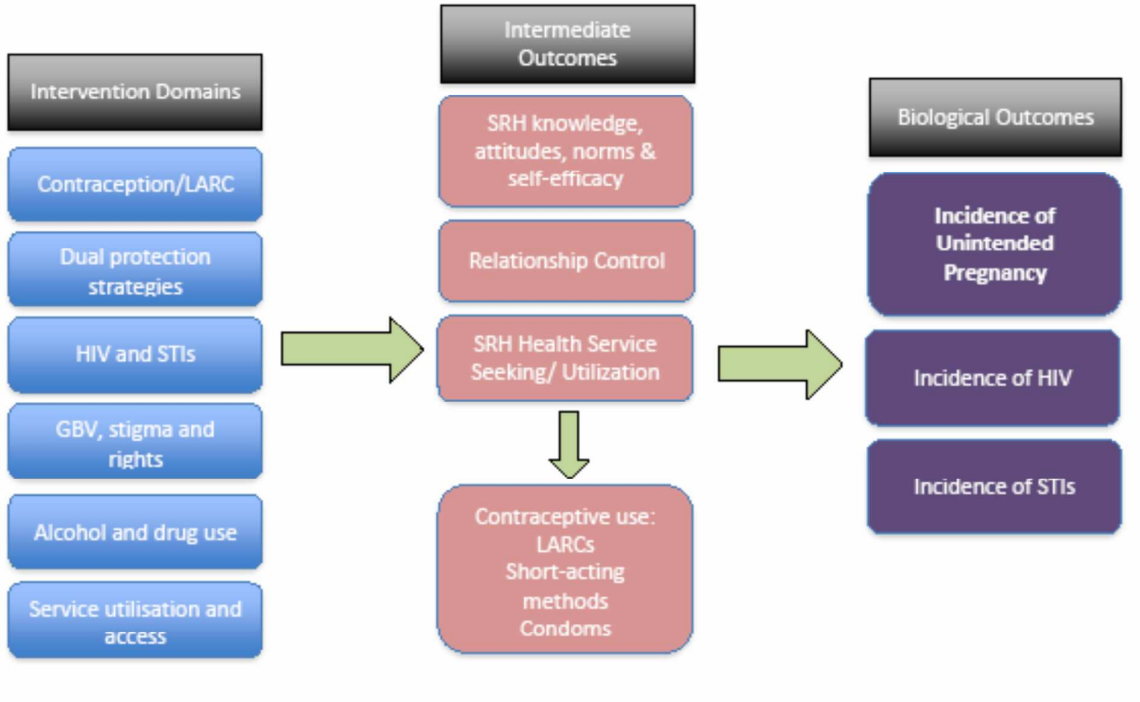
[1] There are some minor variations to these schedules, e.g. an interview reminder and push message during month 6 for logistical reasons.
[2] Messages are charged per 160 characters (1 screen). Messages longer than this will appear as one long SMS on most phones but may be split into multiple messages on older phones.
[3] Each 'month' is 4 weeks, making up 12 calendar months in total

Pull (on-demand) messages	63	160 – 640 characters (2-4 screens)	User determined

11.1 The sexual and reproductive health intervention

The theoretical logic model underpinning the messages is presented below. The primary focus of the message content is dual method contraceptive use and long-acting reversible contraceptives (LARCs). Other domains which are known to impact on FSW's sexual risk behaviour and could plausibly impact on their pregnancy risk include HIV and STI knowledge and prevention, alcohol use, health service utilisation and gender-based violence and rights. These domains were drawn from a literature review done by the study team identifying key SRH issues for sex workers and barriers and motivators to changing risk behaviour.

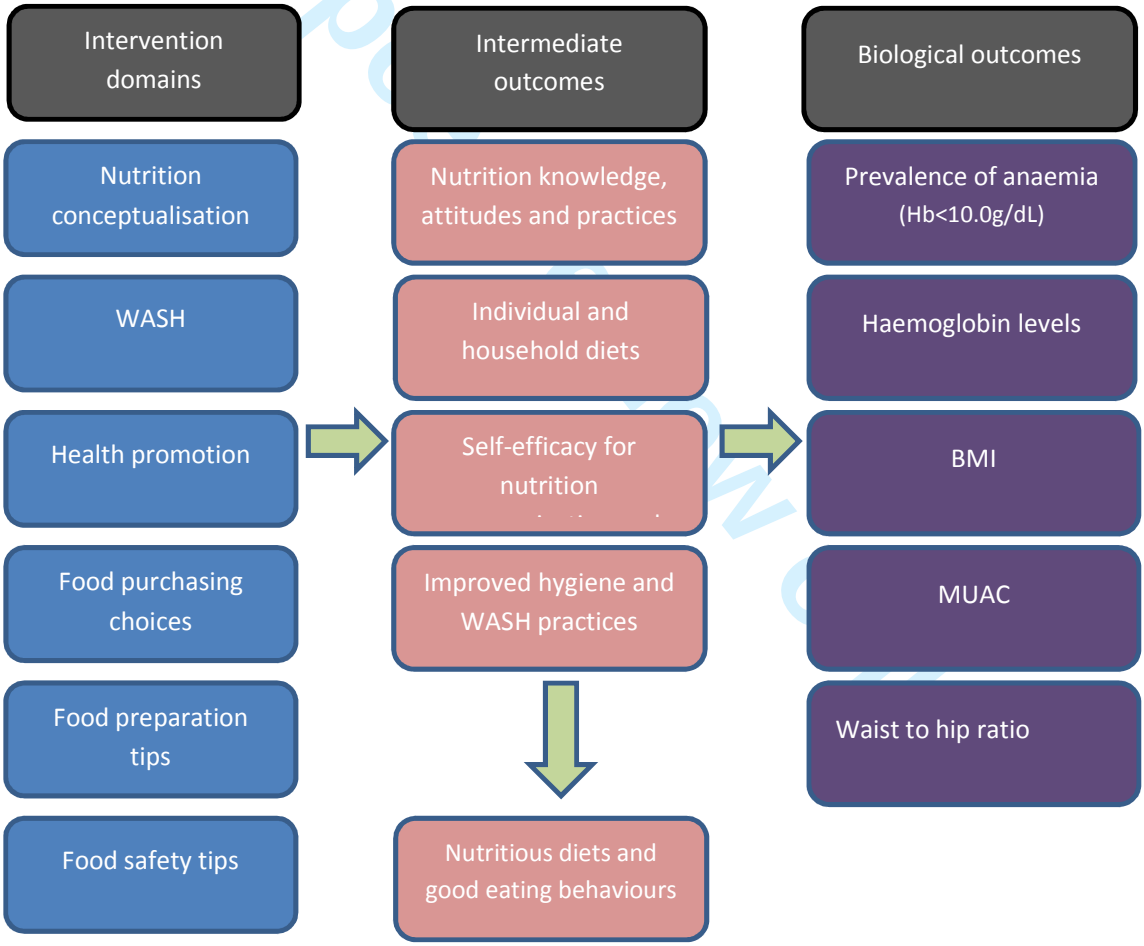
It is predicted that these messages will improve FSWs' knowledge and their self-efficacy for contraceptive use, improve relationship control, for example their ability to negotiate contraceptive use with partners, and increase health-seeking. In turn, these all contribute to increasing contraceptive use. These behavioural and interpersonal factors are known to impact on pregnancy, STIs and HIV acquisition, which are the biological outcomes the intervention aims to address.



11.2 The nutrition intervention

Similarly to the SRH intervention, the nutrition intervention domains are based on a theoretical logic model which is presented below. The primary focus of the message content is consumption of high value nutrient diets, aimed at improved nutritional status, particularly the level iron. Key nutrition domains in the program include conceptualisation of nutrition, food purchasing choices, food preparation tips, food safety tips and food system tips. Other domains considered preconditions for improved nutritional status include water sanitation and hygiene (WASH) and health promotion. The domains are based on formative research with female sex workers in Mombasa and literature review.

It is predicted that these messages will improve knowledge, attitudes, practices and their self-efficacy for improved diets, good eating behaviours, improved hygiene, interpersonal communication and support, and utilisation of available services.



12 Study procedures

12.1 Randomisation

Randomisation will occur at cluster level, with clusters being defined as establishments where FSWs sell sex and have been identified in past research with 248 venues in Changamwe and 263 in Kisauni (National AIDS & STI Control Programme (NASCOP) and National AIDS Council (NAC) 2012).

A two-stage sampling process will be used. At the first sampling stage, FSW venues will be selected proportionate to size and randomised to either control or intervention arms. At the second sampling stage, we will aim to consecutively select 10 FSWs from each randomised venue, based on an estimated average FSW venue cluster size of 12(National AIDS & STI Control Programme (NASCOP) and National AIDS Council (NAC) 2012). At venues where less than 10 FSWs are active, all FSWs from the selected venue will be invited to participate in the study. Sampling of FSW venues will continue and additional venues sampled until the required sample size of 860 women is achieved.

Cluster randomisation will be done centrally and will be 1:1 (intervention and control). Participant responses will be weighted post data collection to account for any variation in relative selection probability due to variability in size of selected clusters. Participants and study team will be blinded to intervention and control allocation until after cluster enrolment is completed and all baseline questionnaires administered for that cluster. Overall, the steps above allow optimal (as random as possible) sampling from the FSW population, but minimises the potential dilution effect of individual randomisation through message sharing.

12.2 Pre-screening

Potential study participants who have been identified at the cluster level will be approached and minimum pre-screening applied. Women who are aged 16 years or older, self-report to have engaged in paid sex work in the last six months, residing and planning to continue to reside within the site-specific catchment area for the next 12 months and who have a personal mobile phone from either Safaricom or Airtel will be invited to participate in the study. Potentially eligible women will receive a card with a unique, anonymous ***referral card number*** (made up of cluster number and sequential participant number for that cluster) and are offered to go to the nearest research clinic (in Kisauni or Changamwe) for full screening of eligibility criteria, consenting and subsequent enrolment as soon as possible and within the next 7 days. It is anticipated that each cluster will be fully enrolled within a 14-day period. The study will document the number of cards that are disbursed at each cluster following pre-screening. No other data will be collected at this stage.

12.3 Screening and enrolment procedures

Study visits will be conducted by trained research personnel at enrolment and after 6 and 12 months in a dedicated research space at 2 local dedicated research clinics linked to health facilities. Volunteers must bring their referral card number with them to undergo the screening process, to ensure that only volunteers selected by the random sampling process can enrol.

At this first presentation at the research clinic, the study will be explained in detail to the volunteers by the investigator or his/her representative. ***Intervention allocation will remain blinded to the study participants and study staff until the cluster is fully enrolled.*** If the volunteer is willing to participate in the study, she will be given the written informed consent form to read. If she is illiterate, the form will be read to her by the investigator in the presence of a witness, who is not involved with the study. Any questions about the study that the volunteer may have will be answered by the investigator. Once the participant is satisfied with the information given about the study, she will be requested to sign the written informed consent form. Illiterate women will be asked to mark their left thumb-print on the form in the presence of the witness. The witness will sign and date the form to confirm that they have read or witnessed the accurate reading of the form to the potential participant.

After the subject signs the informed consent document, the full eligibility criteria will be assessed. A master log of volunteers with referral card number, eligibility criteria, and demographic information will be maintained and kept in a locked/secure location. If the volunteer is not admitted into the study, study staff will document the reason for failing screening. For potential volunteers who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined. Subjects who successfully complete screening will have their referral card number recorded as their ***Study Identification Number (study ID)***.

Additional procedures for enrolment visit include administering the structured baseline questionnaire, clinical examination, urine pregnancy test, STI syndromic management, HIV and Syphilis rapid tests, haemoglobin assessment using haemoglobinometer, Eyenaemia mobile application (see 11.6.3), and blood withdrawal for full haemogram (including Hb, haematocrit, white blood count, and mean cell volume; see also Chapter 11.6 on data collection procedures for more detail).

The results of rapid diagnostic tests done at the baseline (urine pregnancy, haemoglobin measured with a haemoglobinometer, HIV and syphilis), month 6 (urine pregnancy, HIV and syphilis) and month 12 (urine pregnancy, haemoglobin measured with a haemoglobinometer, HIV and syphilis) will be communicated to the participants at the time of the visit. Participants newly diagnosed with HIV will be referred for treatment to specialised centres. Those with positive syphilis rapid test will be treated with benzathine penicillin, consistent with the national STI algorithm (NASCOP 2015). Those with anaemia

(Hb< 12.0 g/dL) will receive 1 month of ferrous sulphate 200mg three times perday and folic acid 5mg/day in accordance with Kenyan national guidelines, as well as a stat dose of albendazole 400mg as presumptive treatment for hookworm. They will also be referred to an appropriate health facility for follow up Hb testing and further investigation as necessary. Those with severe anaemia (Hb < 8.0 g/dL) or significant symptoms of anaemia, will receive an urgent referral for follow up investigations and treatment. Clinical officers will contact women and provide them with a referral if their full blood count reveals macrocytic anaemia (high MCV) or other serious pathology.

Women unable to tolerate the prescribed supplements will be advised to visit their nearest health centre for potential switch to injectable iron supplementation.

For consenting participants, a locator form with Study ID will be completed to potentially track participants for follow-up visits.

Each eligible participant will be registered as a subscriber in the VOTO online platform, and their mobile phone number, study ID and cluster number be will be entered. No other identifying details will be entered into the system.

Once the cluster is fully enrolled (i.e. 10 participants or all participants have enrolled, or the 14 day enrolment period for the cluster has elapsed), the cluster will be randomised to either the SRH or nutrition arm. Each cluster will form a small group in the system, and will be added to the larger SRH or nutrition group after allocation. The intervention, either SRH or nutrition, will commence simultaneously among all participants of one cluster once the cluster is fully enrolled. The intervention will be scheduled to commence in the week following completed enrolment (this corresponds to day 1, when the first WHISPER message will be sent). All members of the cluster will therefore be sent the same messages on the same days throughout the intervention period. The study data manager will have oversight of the use of the VOTO platform, with a limited number of team members given administration access to enter new participants into the system once they are enrolled.

12.4 Follow-up visits (month 6 and 12)

Follow-up visits will be scheduled on month 6 and month 12 after enrolment and completed within a six-week window around the scheduled date, beginning two weeks prior to the target date and extending four weeks after the target date.

Participants will be reminded via SMS three weeks and then one week prior to their face-to-face data collection visit. Women not attending their scheduled visit will be reminded via SMS after one week, followed by a phone call and/or home visit when participants do not attend. For volunteers who do not complete scheduled visits within the allowable window, the visit will be considered “missed” and relevant documentation will be completed to document the missed visit.

During follow-up visits at month 6 and month 12, study procedures will be similar to those at baseline and include administering the structured questionnaire, clinical examination, urine pregnancy test, STI syndromic management, HIV and Syphilis rapid testing, haemoglobin assessment using haemoglobinometer (month 12 only), Eyenaemia mobile application (month 12 only), and blood withdrawal for full haemogram (month 12 only; see Chapter 11.6 on data collection procedures for more detail).

12.5 Unscheduled visits

Additional visit(s) outside of scheduled study visits may be arranged at the discretion of the investigators. Interim visits may occur when the participant has questions for study staff, for interim assessment of pregnancy, Hb, HIV/STI and/or treatment in response to symptoms, or for other reasons at participant's request.

All interim contacts and visits will be documented on the study documents.

12.6 Data collection procedures

The below table outlines the data being collected as part of the randomised trial during scheduled visits.

Table 1: Study assessments among intervention and control participants during follow-up

	Female Sex Workers' study visits		
Assessments	**Month 0**	**Month 6**	**Month 12**
General procedures			
Informed consent procedure (written consent obtained at baseline only)	▯	▯	▯
Eligibility assessment	▯		
Study ID allocation	▯		
Mobile phone registration	▯		
Structured self-report questionnaire	▯	▯	▯
Qualitative inquiry (subgroup of participants from SRH intervention arm only)			▯
Clinical examination			
Nutritional anthropometric assessment	▯	▯	▯
Syndromic STI management	▯	▯	▯
Biological assessment			
Urine pregnancy testing	▯	▯	▯

Haemoglobin using haemoglobinometer	▯		▯
Full Haemogram including haemoglobin, haematocrit and Mean Cell Volume	▯		▯
Haemoglobin using Eyenaemia mobile application	▯		▯
HIV testing, syphilis testing (including pre- and post-test counselling)	▯	▯	▯

12.6.1 Structured face-to-face interviews

Questionnaires have been developed in English, and are based on previously validated measurement tools where feasible, and translated into Swahili.

The baseline questionnaire (annex 5) will ask for detailed socio-demographic information including age, general sexual and reproductive history, sex work, employment, income, family and living circumstances, education, literacy, health and illness, and information about current and past partners.

In addition, questions will ask about pregnancy; pregnancy intentions; contraception and condom use (including dual protection); reasons for discontinuation/non-use of contraception; contraceptive self-efficacy; sexual and reproductive health seeking and service utilisation; sexual risk behaviours; HIV/STI symptoms; sexual and reproductive health knowledge and attitudes; relationship control and joint-decision-making with non-paying emotional partners; dietary intake; perception of body image; nutrition-related health seeking and service utilisation; and food- and hygiene-related knowledge and behaviours.

12.6.2 Clinical examinations

12.6.2.1 Nutritional anthropometric assessments

At baseline, 6 months and 12 months, trained study nurses will conduct anthropometric measurements to assess the nutritional status including weight, height, waist circumference, hip circumference, and mid upper-arm circumference (MUAC).

Weight measurement

All participants will be weighed twice using a validated instrument, such as a bench sale. The scale must be placed on an even, uncarpeted area and levelled with the aid of its inbuilt spirit level (if a zero [0] appears in the display window, the scale is level). Participants are to be weighed without shoes and dressed in light clothing. The participant will be requested to step on the scale and upright in the middle of the platform, facing the research assistant, looking straight ahead with the feet flat and slightly apart until the reading was taken. The research assistant then records the reading in the space provided in the clinical examination form. The weight is recorded to the nearest 100g. The participant is then requested to step off the scale. After the participant steps down from the scale, the research assistant must

wait for the zero reading to appear on the digital display before repeating the procedure. The two readings must not vary by more than 100g. If they do, the scale has to be checked for accuracy, and the procedure repeated until the two readings agree within 100g. If agreement cannot be reached, and the two measurements differ by more than 100g, a third measure must be taken. The two measurements that were nearest to each other will be selected for further analysis.

Height measurement

Standing height will be measured using a stadiometer, see example figure below. The stadiometer is placed on an even, uncarpeted area and the participant's shoes removed. If the hair is tied up on the top of the head, it must be released and the participant positioned facing the research assistant and looking straight ahead with head in the Frankfurt plane. The participant's shoulders should be relaxed, with shoulder blades, buttocks and heels slightly touching the stadiometer's stand, arms relaxed at sides, legs straight and knees together, and feet flat, heels touching together. The measurement then recorded in the space provided in the clinical examination form and the procedure repeated once. Two readings are taken and the measurements were repeated. A third measurement must be taken if the two readings varied by more than 1 cm. The two measurements closest to each other were used for further analysis.

Figure 1: Measuring height of participants

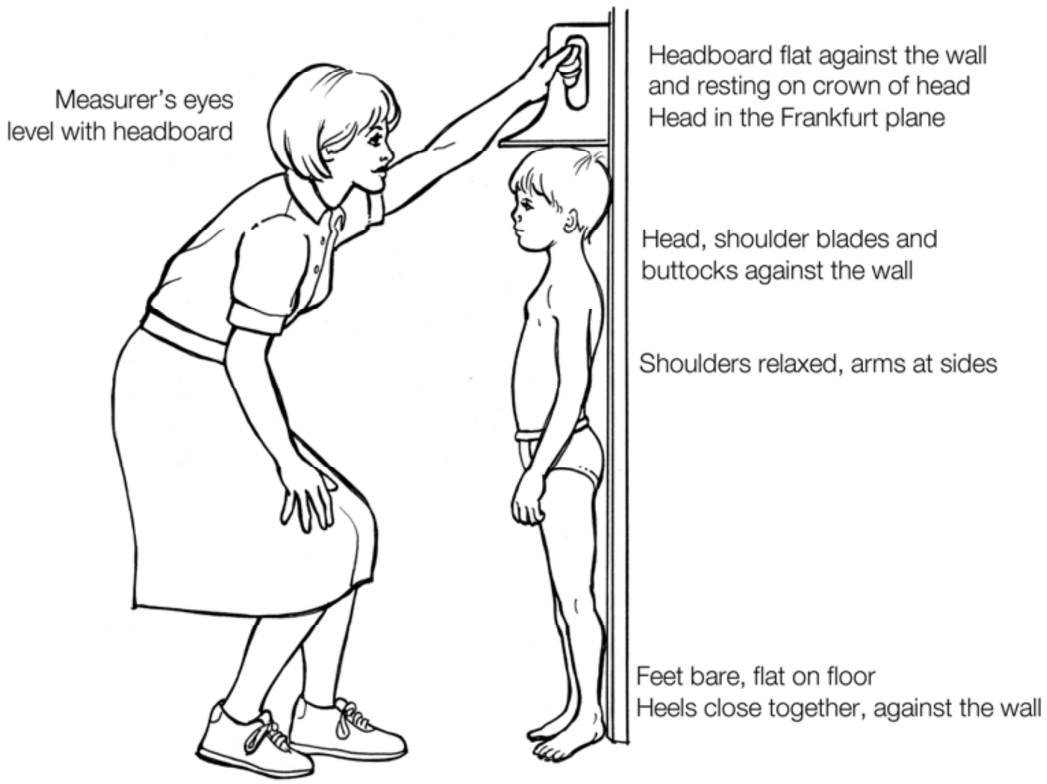
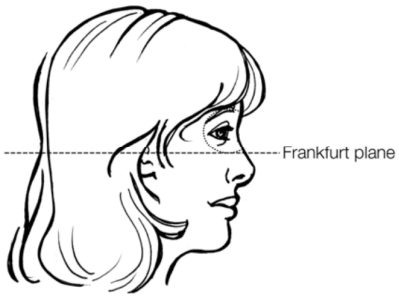


Figure 2: The Frankfurt plane is defined by a line from the most superior point of auditory canal to the most inferior point of infraorbital rim (eye socket/hard bony rim underneath the eye).



Body mass index

The body mass index (BMI) will be calculated for all participants and the recommended CDC/WHO cut-offs used to ascertain underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5 > 25.0 kg/m^2), overweight (BMI ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2). This result will not be communicated to participants.

Waist circumference measurement

The participant should stand erect, with the abdomen relaxed, arms at the sides, feet together, and her weight equally divided over both legs. The lowest rib-margin and the iliac crest will be identified in the mid-axillary line. The level of the waist circumference is defined as the midpoint between the two anatomical landmarks and measured by positioning a non-stretch fibreglass tape (Seca Model 203; Medical Scales and Measuring Systems) horizontally round the abdomen. Participants will be asked to breathe normally and to breathe out gently while the measurement was being taken so as to prevent them from contracting their muscles or holding their breath. The measurement is taken without the tape compressing the skin. The reading is taken to the nearest 1cm. Two measurements will be taken and recorded in the appropriate section of the clinical examination form. If the two measurements differ by more than 1cm, a third measurement was taken. The two measurements that were nearest to each other will be used for further analysis (Lohman, Roche et al. (eds) 1988; Jones, Hunt et al. 1986).

A waist circumference > 88.0 cm in women indicates central obesity. This result will not be communicated to participants.

Hip circumference measurement

Participants must stand erect and positioned as for the measurement of the waist circumference with arms at the sides and feet slightly apart. The measurement is taken at

the point yielding the maximum circumference over the buttocks (Jones, Hunt et al. 1986) with the tape held in a horizontal plane, touching the skin but not indenting the soft tissue (Lohman, Roche etal. (eds) 1988). The measurement is taken to the nearest 1cm. Two measurements are taken and recorded in the appropriate section of the clinical examination form. If the two measurements differ by more than 1cm, a third measurement is taken. The two measurements that were nearest to each other are selected for further analysis.

Waist-to-hip ratio

The waist-to-hip ratio will be calculated by dividing the waist circumference by the hip circumference. Values of > 0.8 are regarded as indicative of central obesity. This result will not be communicated to participants.

Mid-upper arm circumference (MUAC)

MUAC is the circumference of the left upper arm, measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromium).
As MUAC is less affected than BMI by the localised accumulation of excess fluid (pedal oedema, periorbital oedema, ascites) common in famine, it is likely to prove to be a more sensitive index of tissue atrophy than low body weight. It is also relatively independent of height. Values of <185mm and <160mm will be used to denote moderate and severe undernutrition respectively.

12.6.2.2 Syndromic STI management

During their clinical assessment, participants will ask about their experience of recent STI-related symptoms, under the main syndromic categories as per World Health Organisation guidelines (genital ulceration, abnormal vaginal discharge, vaginal itching/burning, groin lump, lower abdominal pain). If they report symptoms, they will be given STI counselling and have a vaginal examination (and abdominal examination if indicated) as per the WHO guidelines. Participants with evidence of an STI syndrome will be provided with the recommended treatment and referral for further investigation if indicated.

12.6.3 Biological investigations

Trained study nurses will obtain urine samples for pregnancy testing, and blood samples for full haemogram (including WBC, WBC differential, Hb, Ht, MCV, MCH, MCHC, Platelets, RBC), rapid haemoglobin test (using haemoglobinometer), syphilis and HIV. Moreover, assessment with the novel Eyenaemia application on mobile phone will be administered.

Urine pregnancy testing

Urine pregnancy testing will be done at baseline (as part of eligibility screening) and during follow-up at month 6 and month 12. The test will be done to detect the presence of the human chorionic gonadotropin (hCG). The hormone is produced by the placenta shortly after the embryo attaches to the uterine lining. It builds up rapidly in the body within the first few days of pregnancy or implantation, most but not always about 6 to 12 days after fertilisation.

HIV testing

Pre- and post-test counselling will be conducted as per standard care by certified counsellors. HIV testing will be done by Determine® HIV-1 and First response® HIV-1 Rapid Tests conducted. Only those wishing to know their HIV status will receive post-test counselling (participants may decide not to know the results of HIV testing). Sex workers who test HIV positive at a visit will be considered HIV-infected and not have additional HIV tests at subsequent follow-up visits.

Syphilis

Syphilis serologic screening will be done using a rapid Treponema pallidum haemagglutination (TPHA) test. Those found positive will be treated with a stat IM injection of Benzathine Penicillin. Pregnant women found to be positive on TPHA will be provided treatment and referred for specialist follow-up. ***Anaemia assessments***

Various assessments will be done to determine haemoglobin. Firstly, a point-of-care haemoglobin test will be performed at baseline and at the 12-month follow-up visit using a haemoglobinometer. The test result will be communicated as soon as the result is available. Participants with anaemia will receive iron and folic acid supplementation, and presumptive hookworm treatment, and referred for follow-up as described in section 12.3.

Secondly, a 5mL blood sample will be drawn and sent for assessment of a laboratory-based full haemogram, including Hb, haematocrit, white blood count, and mean cell volume. Blood samples will be kept in a cooler box containing ice packs, and couriered daily, in a cooler box containing ice packs, to reach the appointed laboratories within 24 hours from the time a blood sample was collected for biomarker analysis.

This assessment is used as the gold standard Hb test and used for the primary outcome assessment of the nutrition intervention. Moreover, this (gold standard) test result will be used for calibration and validation of the Eyenaemia mobile application (see below). The results of the haemogram will not be communicated to participants, unless it reveals unexpected and significant pathology such as macrocytosis or very high white cell count, in which case participants will be contacted and referred accordingly. Results from the validated and approved haemoglobinometer will be communicated to participants at the point of testing.

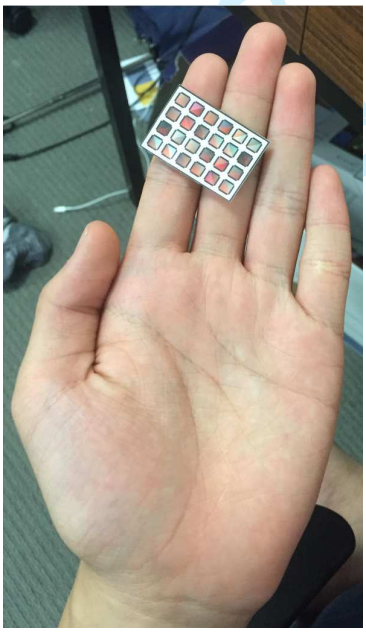
Eyenaemia mobile application (sub-study)

This assessment will address the secondary objective to assess performance, feasibility and acceptability of a mobile phone administered application for measuring anaemia. Each of the study teams will have two study phones (four in total) with the Eyenaemia application installed to assess anaemia. Participants will be requested to fill out a separate consent form (annex 3) for this assessment and results will not be communicated to the participants. Instead, results from the validated and approved haemoglobinometer will be communicated to participants.

At enrolment, and at month 12, each participant will have Eyenaemia assessments from the left conjunctiva (2 pictures) and right conjunctiva (2 pictures) as well as both the hand palms.

The Eyenaemia application estimates anaemia levels via photos taken of the participants' conjunctiva with a colour standard in view (see photo 1). Photos as part of the study will be collected using the front or rear view camera of one of the *study phones* operated by the study nurses. Each of the study phones will run Windows 10 mobile with full disk encryption and passcode authentication, and will be secured with Avast Anti-theft to allow remote deletion of all data.

Photo 1: Palm photo with colour standard used for Eyenaemia mobile application.



Once photos are captured they will be immediately uploaded to the *Eyenaemia server.* Photos are encrypted on the server so that unauthorised personnel cannot view them. Once photos have been processed for quality assurance, photos will be cropped such that identifying features will be removed (see photo 2).

Photo 2: Photo of cropped conjunctiva with colour card as stored with no identifying features.

Photos may be retained for a short period of time on the *study phone* pending upload, in encrypted memory storage. Once uploaded, the photos will be erased from local storage on the *study phone.* All photos will be transmitted across the web using *HTTPS* with TLS 1.2 encryption. Each photo will be identified using the patient's anonymous and unique study identifier.

Metadata associated with the photo will be collected, including *Username of data collector, IP address*, *Device UID*, as well as time taken will be stored upon the *Eyenaemia server.* Complete photos will only be retained on the server until they have passed quality control procedures. Quality control is done as follows:

Number of photos	Review time
0 - 300	Daily
300 - 600	Twice weekly
600 - 1200	Weekly
1200 - completion	Fortnightly

Otherwise, long term data will only consist of extracted conjunctiva (photo 2), palm and colour standard, as well as aggregated statistics.

12.6.4 Participant follow-up

Participants will be reminded via SMS three weeks and one week prior to their face-to-face data collection visit. Women not attending their scheduled visit will be reminded via SMS after one week, followed by a home visit when participants do not attend.

12.6.5 Referral to services and treatment of anaemia

Participants with anaemia with anaemia (Hb< 12.0 g/dL) based on the haemoglobinometer result will receive 1 month of ferrous sulphate 200mg three times per day and folic acid 5mg/day in accordance with Kenyan national guidelines, as well as a stat dose of albendazole 400mg as presumptive treatment for hookworm. They will also be referred to an appropriate health facility for follow up Hb testing and further investigation as necessary. Those with severe anaemia (Hb < 8.0 g/dL) or significant symptoms of anaemia, will receive an urgent referral for follow up investigations and treatment at the district hospital. Women unable to tolerate the prescribed supplements will be advised to visit their nearest health centre. Study clinicians will contact women and provide them with a referral if their full blood count reveals macrocytic anaemia (high MCV) or other serious pathology.

Participants with any other relevant medical conditions requiring attention will be identified during study visits, and referred to their nearest health centre for further examination and care.

12.7 Participant withdrawal

Participants may voluntarily withdraw from the study for any reason at any time during the study. At any time, a participant can inform the investigator that she is no longer willing to

receive the messages, and withdrawal will be implemented as soon as feasible in the VOTO system (no more than 14 days after the initial request).

The Investigator may also withdraw volunteers from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Volunteers may be withdrawn from the study if relevant government or regulatory authorities, or site Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) terminate the study prior to its planned end date. Every effort will be made to complete a final evaluation of volunteers who withdraw or are withdrawn from the study prior to completing follow-up. Study staff will record the reason(s) for all withdrawals in volunteers' study records.

13 Data management and statistical analysis

In the trial, all participants will be given a unique identification number to link their data. Questionnaires will be developed in English, translated into local language (Kiswahili), and then piloted before use. Data will be captured and managed electronically using handheld tablets with REDCap (Research Electronic Data Capture) software. REDCap provides a secure and intuitive interface for users to enter data and allows real time validation rules (with automated data type and range checks) at the time of entry. Data collected in the course of the research are managed by the program, and can be analyzed by commonly used statistical packages, including SAS, Stata, SPSS, and R. REDCap has a flexible and fine-grained authorisation matrix, and will allow different members of the study team to have different levels of access (none, read-only or edit) to data entry forms, and access to database management and data export tools. Provisions will be put in place to restrict access to data export to allow export of de-identified data only. REDCap includes full audit trail, recording all operations on the data, including viewing and exporting. The audit log records operation, date and time, and the user performing the operation, permitting review of the audit trail as necessary. REDCap enforces data integrity protection by design; all "databases" created by users are logical data sets on top of relational database with built-in integrity protection controls.

SMS data, and in particular data related to accessing the on-demand component, will be automatically collated on an online server, and then imported into the database. The data will be checked for consistency using common software and procedures, and any errors, inconsistencies and unexpected values in the data will be noted and queried with the clinic investigators and resolved or confirmed as rapidly as practical. A electronic audit trail will be kept of all changes made to the study database.

Hard-copy study documentation will be kept securely as study source documents for potential review and/or audit during or until 7 years after the study ends. Participating women's consent forms and enrolment log will be kept separately in locked cabinets in participating clinics, and at the local data management centre. Only the Principal Investigators, study co-ordinator and authorised study personnel will have access.

13.1 Sample size

The sample size was calculated to obtain sufficient power to examine the effects of the SRH intervention. The sample size formulae are shown in figure 3 below.

Based on a 12-month incidence of unintended pregnancy of 27% in the control group (data from our previous research in the study area) (Bosire, Okal et al. 2009), and in order to detect a 37% relative reduction in annual unintended pregnancy incidence (hazard risk=0.63), with 80% power (5% significance level), we will enrol 860 participants from a minimum of 86 FSW venues – 430 participants per arm. This estimate is adjusted for an

expected 10% attrition rate and estimated inflation in standard error due to cluster randomisation (deff=1.18: estimated ICC=0.02,(Cai, Shi et al. 2010) cluster size=10).

$$E = \frac{\left(z_{1-}\frac{\alpha}{k} + z_{1-}\beta\right)^2}{\pi_1(1-\pi_1)\ln^2(\Delta)} \quad (1)$$

$$p_E = 1 - \{S_1(T) + S_2(T)\}0.5 \quad (2)$$

$$N = \frac{E}{p_E} \quad (3)$$

$$D_{eff} = 1 + (\overline{m} - 1)\rho \quad (4)$$

Figure 3: Sample size formulae. Events for a given effect size (hazard ratio), exposure distribution and type I and II error rate (1); overall probability of failure (2) given hazard ratio; required number of observations given overall probability of failure (3) and design effect (inflation factor) given expected cluster size and between cluster heterogeneity (4).

Sample size estimates were not done for the nutrition trial arm. Estimates of anaemia among the local sex work population are not available to inform a sample size calculation with any precision. The sample size in this trial is, however, considerably larger than another trial in Kenya which aimed to reduce anaemia by providing iron supplements alone. That study, among 470 postpartum women was able to detect a difference in mean haemoglobin between the two study arms (Mwangi, Roth et al. 2015).

13.2 Statistical analysis and reporting

A detailed scheme of analysis will be developed at a later date while the study is ongoing. We outline in this section some of the principles, which will be used to guide decisions during data analysis. Analysis methods will, as far as possible, follow the CONSORT guidelines (Moher, Schulz et al. 2001).

Primary analysis will compare the primary endpoints (either unintended pregnancy incidence, or anaemia prevalence) between groups at 12 months and secondary analysis will compare groups at 6 months.

Given the interval-censored nature of unintended pregnancy incidence, discrete-time survival models using generalised linear modelling will be used to compare unintended

pregnancy incidence between FSW exposed to SRH intervention and those exposed to nutrition intervention messages.

These analyses will provide estimates with robust standard errors for FSW venue clustering. Standardised probability weighting will be applied in population-averaged analyses to account for any sampling bias where achieved sample cluster sizes vary. Where randomisation is not effective in removing allocation bias, adjusted models will be specified. In all analyses, associations will be considered statistically significant at the 5% level. The statistician will conduct the analysis blind to the intervention group.

Our secondary analyses will employ a per-protocol approach to evaluate differences in primary and secondary outcomes. These analyses will resemble the intent-to-treat analyses described above, with the difference that individuals will be evaluated based on the number of messages of intervention exposure they received (as reported by women or as measured by cell phone company reports). As above, these analyses will account for the clustering of results within sites and include use of causal inference methods to adjust for potential confounding. These analyses will allow us to determine whether an observed effect of the intervention is limited due to inadequate implementation and whether there is a needed 'dosage' for the interventions to successfully impact outcomes. This will also permit any accounting for contamination should a control-group participant also have received access to intervention messages of the other group.

Reporting of findings will adhere to the 2016 Guidelines for reporting of health interventions using mobile phones (see checklist below) (Agarwal, LeFevre et al. 2016).

Table 1 | mHealth evidence reporting and assessment (mERA) guidelines, including mHealth essential criteria

Criteria	Item no	Notes	Page no where item is reported
Infrastructure (population level)	1	Clearly presents the availability of infrastructure to support technology operations in the study location. This refers to physical infrastructure such as electricity, access to power, connectivity etc. in the local context. Reporting X% network coverage rate in the country is insufficient if the study is not being conducted at the country level	
Technology platform	2	Describes and provides justification for the technology architecture. This includes a description of software and hardware and details of any modifications made to publicly available software	
Interoperability/ Health information systems (HIS) context	3	Describes how mHealth intervention can integrate into existing health information systems. Refers to whether the potential of technical and structural integration into existing HIS or programme has been described irrespective of whether such integration has been achieved by the existing system	
Intervention delivery	4	The delivery of the mHealth intervention is clearly described. This should include frequency of mobile communication, mode of delivery of intervention (that is, SMS, face to face, interactive voice response), timing and duration over which delivery occurred	
Intervention content	5	Details of the content of the intervention are described. Source and any modifications of the intervention content is described	
Usability/content testing	6	Describe formative research and/or content and/or usability testing with target group(s) clearly identified, as appropriate	
User feedback	7	Describes user feedback about the intervention or user satisfaction with the intervention. User feedback could include user opinions about content or user interface, their perceptions about usability, access, connectivity, etc	
Access of individual participants	8	Mentions barriers or facilitators to the adoption of the intervention among study participants. Relates to individual-level structural, economic and social barriers or facilitators to access such as affordability, and other factors that may limit a user's ability to adopt the intervention	
Cost assessment	9	Presents basic costs assessment of the mHealth intervention from varying perspectives. This criterion broadly refers to the reporting of some cost considerations for the mHealth intervention in lieu of a full economic analysis. If a formal economic evaluation has been undertaken, it should be mentioned with appropriate references. Separate reporting criterion are available to guide economic reporting	
Adoption inputs/ programme entry	10	Describes how people are informed about the programme including training, if relevant. Includes description of promotional activities and/or training required to implement the mHealth solution among the user population of interest	
Limitations for delivery at scale	11	Clearly presents mHealth solution limitations for delivery at scale	
Contextual adaptability	12	Describes the adaptation, or not, of the solution to a different language, different population or context. Any tailoring or modification of the intervention that resulted from pilot testing/usability assessment is described	
Replicability	13	Detailed intervention to support replicability. Clearly presents the source code/screenshots/ flowcharts of the algorithms or examples of messages to support replicability of the mHealth solution in another setting	
Data security	14	Describes the data security procedures/ confidentiality protocols	
Compliance with national guidelines or regulatory statutes	15	Mechanism used to assure that content or other guidance/information provided by the intervention is in alignment with existing national/regulatory guidelines and is described	
Fidelity of the intervention	16	Was the intervention delivered as planned? Describe the strategies employed to assess the fidelity of the intervention. This may include assessment of participant engagement, use of backend data to track message delivery and other technological challenges in the delivery of the intervention	

14 Ethical considerations

14.1 Consent

Written informed consent will be obtained from each study participant prior to full screening assessment. Women aged 16 and 17 years will be considered mature minors and able to consent, without involving parents and guardians due to the sensitive nature of the subject matter.

Informed consent forms will be available in both Kiswahili and English. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A thumbprint witnessed by a person independent from the study staff may replace signature. Volunteers will be provided with a copy of their informed consent forms if they are willing to receive them. Study staff will document the informed consent process.

14.2 Confidentiality

All study-related information will be stored securely at the study site. All volunteer information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by coded number only to maintain volunteer confidentiality. All computer entry and networking programs will also be done by coded number only, and all local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link Volunteer ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Volunteers' study information will not be released without written permission of the volunteer, except as necessary for data monitoring purposes by Burnet Institute, or regulatory authorities.

Although the study site will make every effort to protect the privacy and confidentiality of all study volunteers, it is possible that volunteers' involvement in the study could become known to others, and that social harms may result. For example, volunteers identified during the study as being HIV-positive could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

14.3 Risks

Study volunteers when undergoing phlebotomy may experience discomfort, feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.

There is a risk that discussion of personal and sensitive topics may result in psychological distress for participants. Questions may trigger memories of past trauma, including previous unintended pregnancies, abortion, relationship difficulties, sexually transmitted infections or physical or sexual violence. These kinds of traumatic experiences are known to be

common among FSWs in Kenya. Participants who experience significant distress will be offered counselling free of charge and/or referral for other relevant services. Participants do not have to answer any questions if they chose not to, and they are free to withdraw at any time. This will be emphasised by the researchers during the consent process, and reiterated during the interview. Breaks will also be offered during the interview if the participant appears uncomfortable.

Volunteers may also become embarrassed, worried, or anxious when completing their HIV-related interviews and/or receiving HIV counselling. They also may become worried or anxious while waiting for their HIV test results or after receiving HIV-positive test results. Trained counsellors will be available to help volunteers deal with these feelings.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that volunteers' involvement in the study could become known to others, and that social harms may result (i.e., because volunteers could become known as sex workers). A previous randomised trial on integrating mobile phones into medical abortion provision in South Africa noted that 20% of participants were worried about phone privacy (de Tolly and Constant 2014).

In such events, volunteers could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Volunteers also could have problems in their partner relationships associated with use or attempted use of family planning methods and/or condoms, as advocated in HIV risk reduction counselling messages, including the potential for physical, financial, and/or emotional harm. Study staff will make every effort to facilitate resolution of such problems, including provision of follow-up counselling for the participant, her partner, or both together as a couple, as well as providing referrals to other relevant services that may be available in the study site community.

14.4 Benefits

There may be no direct benefits to volunteers in this study. However, volunteers and others may benefit in the future from information learned from this study. Study volunteers will receive syphilis testing, HIV counselling and testing, and will be provided with condoms and syndromic STI treatment in accordance with WHO guidelines, free-of-charge. Participants with anaemia (Hb<12.0 g/dL) will be given 1 month's supply of iron and folate supplements. Those with moderate or severe anaemia will be referred to the district hospital.

For other medical conditions identified as part of the study screening and/or follow-up procedures, volunteers will be referred to other sources care available in their community.

At each scheduled study visit, participants will receive a financial reimbursement for transport costs and time of 400 Kenyan shillings (approximately 5 Australian dollars).

15 Study limitations

Sex workers in one study arm may communicate with those in the other arm about the messages received and even share the messages. Women in the two groups may also discuss with each other new knowledge gained or changes in behaviours stemming from the messages received. This would introduce contamination between the two arms, and thus diminish the ability to detect a difference in effectiveness between the two groups. We will attempt to reduce this by recruiting sex workers in clusters, based on the venues where they work. This strategy may only be partially effective as sex workers are a highly mobile population and likely work from several venues. However, as we are recruiting only a portion of sex workers in the area (from 86 out of 511 hot spots), this diminishes the chances of sex workers from each arm interacting with each other. We will attempt to measure this potential bias by asking women if they shared messages with others, and specifically women in the other study arm.

The SRH arm focuses on addressing the sex workers demand for family planning services and on improving the use of contraception they receive (for example by optimising adherence). However, many of the barriers to family planning stem from deficiencies in health services (supply side issues). This may concern stockouts of commodities, providers not offering women a choice of methods, and even health worker disrespect and abuse of patients. The supply-side problems are not directly addressed in the study intervention, and this may limit the potential increases in family planning coverage in this population.

16 Qualitative assessment of SRH intervention

An embedded qualitative study will be conducted as part of the intervention evaluation, consisting of one-on-one interviews with a sample of participants in the SRH intervention arm and their emotional partners. The interviews will include both women who become pregnant over the course of the trial as well as those who did not. Similarly, we will include emotional partners of women who did and did not conceive during the trial.

The qualitative enquiry will focus on examining the acceptability and feasibility of the intervention (secondary objective of the SRH intervention; 8.2.2). Interviews will explore both positive and negative attributes of the SRH intervention, and explore in depth how the intervention influenced the attitudes, behaviours and practices of female sex workers relating to sexual risk behaviour, family planning and access to family planning services. Moreover, we will explore how this influenced the relationship between participants and their partner(s). Women in the nutrition arm will not be included in the qualitative interviews.

Fifteen to twenty women who did not become pregnant, and eight to ten women who conceived during the study will be invited to be interviewed. More women who did not conceive will be invited in order to delineate the processes through which the intervention worked. Also, ten to twelve male partner interviews are anticipated. For all sub-populations included in this study component, fewer than the maximum number of interviews will be completed if the study team believes that data saturation has been reached.

16.1 Qualitative research specific objectives

1. To assess the feasibility and acceptability of the SRH mHealth intervention
2. To examine if and how the intervention influenced FSWs' attitudes and beliefs about pregnancy risk and prevention, and their degree of control and negotiating power over their sexual relationships, and how these factors influenced their uptake of contraceptives
3. To explore the role of FSWs' emotional partners in facilitating or preventing the uptake of dual method contraceptives, and the influence of the intervention on this role
4. To explore potential risks and benefits of involving emotional partners in future health promotion initiatives aimed at improving FSWs' sexual and reproductive health.

16.1.1 Qualitative research questions

For more detail, see the qualitative research interview guides (annexes 7-9)

Objective 1 [interviews with women]

1. Is SMS an acceptable means of providing information about family planning?

2. Did WHISPER reach its target audience appropriately and successfully?
3. How did participants use or act on WHISPER messages, information and advice?
4. How did participants respond to the user interface and mode of delivery?

Objective 2 [interviews with women]

1. Why did/didn't women take up contraception or switch methods during the study? To what extent were these actions mediated by the WHISPER intervention?
2. [Participants who conceived]: Why do participants think they became pregnant, did this follow a change in contraceptive use, and to what extent was this change influenced by WHISPER?
3. How could WHISPER have provided better information or had a greater influence on pregnancy prevention?
4. How did the use of WHISPER influence FSWs' relationships with emotional partners, clients and health providers?
5. Did FSWs experience any conflict with partners, family, peers or others as a result of being involved in WHISPER?

Objective 3 [interviews with women and men]

1. [Men and women]: To what extent were messages shared and discussed with emotional (non-paying) partners?
2. [Men and women]: What role did emotional partners play in pregnancy prevention? Did this change during the trial?
3. [Men, if viewed partners' messages or discussed them]: How did men respond to the intervention? What did they like/dislike?
4. [Men]: How did men's attitudes towards pregnancy and their partners' sexual health change during the study?
5. [Women]: To what extent do FSWs want their partners to be involved in pregnancy prevention?

Objective 4 [interviews with women and men]

1. [Men]: How interested are emotional partners in FSWs' risk of pregnancy, and to what extent do they want to be involved in pregnancy prevention?
2. [Men]: How could male partners be encouraged to have greater knowledge of pregnancy risk and greater involvement in pregnancy prevention?
3. [Men]: Would male partners want to receive SRH information via mobile?
4. [Women]: what are the risks of involving male partners in an intervention like WHISPER?

16.2 Qualitative research methods

16.2.1 Qualitative study design

Interviews will be conducted with purposively selected trial participants and a small number of participants' emotional partners. Women who are invited to participate will also be given an invitation letter for their partners. Information provided by women and male partners will not be linked or shared with the participants. Interviews with FSWs will be conducted by trained female researchers, and trained male researchers for interviews with male partners. Interviews will be offered in Swahili or English (as per the participant's preference).

Interview guides have been developed for each participant group (annexes 5-7). Interviews will be conducted with sufficient time for reflection and discussion between interviews, to facilitate an iterative approach to data collection.

16.2.2 Data analysis

Interviews will be transcribed verbatim and translated into English when conducted in Kiswahili. Data will be imported into a qualitative data analysis program, e.g. Nvivo, for thematic analysis. Transcripts will be coded inductively, clustered to reflect emerging themes, and checked for consistency of interpretation.

The qualitative analysis will form part of the broader evaluation of WHISPER, with effectiveness of the intervention determined by assessing primary and secondary quantitative SRH outcomes at 12 months. Qualitative findings will provide a more detailed picture of the acceptability and feasibility of the intervention, provide context to key quantitative findings, and explore participants' responses to the intervention and the mechanisms by which the intervention was or was not effective.

16.2.3 Ethical issues

Written informed consent will be separately obtained from all participants invited to participate in the qualitative interviews (consent forms annex 2). As for the RCT enrolment, 16- and 17- year old volunteers will be considered mature minors and able to consent, without involving parents and guardians due to the sensitive nature of the subject matter. Illiterate volunteers will be eligible to take part, and will consent by providing a thumbprint witnessed by an independent person of their choosing.

Women who are comfortable with their partners being contacted for an interview will be given an invitation letter for their partners. It will explain that the woman and her partner will be interviewed by different researchers and that any information revealed in the interview will not be disclosed to the other partner.

All audio and handwritten data collected from the workshops and interviews will be stored securely. Electronic notes, transcripts and translations will be stored electronically and

password-protected. Only members of the qualitative research team will have access to these documents. Consent forms containing identifying details will be kept physically separate from the other data collected, and stored in a locked filing cabinet. The informed consent forms will not reveal the fact that participants are involved in sex work. Pseudonyms will be allocated to all participants and will be used throughout the analysis and reporting to protect participants' confidentiality.

16.2.3.1 Disclosure of sex work status to male participants

To protect the privacy of the FSW participants, the interviewer will not reveal that they know the sex work status of the male participants' partners. Sex work may be discussed in the interviews with men generically, but not specifically in relation to their partner. The study will be presented as one aiming to understand men's views of sexual and reproductive health, relationships and pregnancy prevention.

16.2.3.2 Risks of participation

There is a moderate risk that discussion of personal and sensitive topics may result in psychological distress for participants, in particular FSWs. Memories of past trauma, including previous unintended pregnancies, abortion, relationship difficulties, sexually transmitted infections or physical or sexual violence, may be triggered by the discussion. These kinds of traumatic experiences are known to be common among FSWs in Kenya. Similar trauma may have been experienced by participants' male partners. The latter may also have more difficulty discussing topics like SRH and sexual relationships than FSWs, for whom they are part of working life and discussed among peers.

Participants who experience significant distress will be offered counselling free of charge and/or referral for other relevant services. Participants do not have to answer any questions if they chose not to, and they are free to withdraw at any time. This will be emphasised by the researchers during the consent process, and reiterated during the interview. Breaks will also be offered during the interview if the participant appears uncomfortable.

While there is a risk that some participants may become distressed, others may benefit from the opportunity to talk about personal issues with an independent person in a safe, private, non-judgmental environment.

17 Timeline

It anticipated that study recruitment and enrolment commences on 15 July 2016, with last enrolment anticipated 6 months later and final follow-up visit in December 2017.

WHISPER-SHOUT Study timelines	2016				2017				2018			
Stakeholder/community engagement; protocol & questionnaire design/pre-testing; capacity building/training												
Ethics approval obtained												
Enrolment/collect baseline data, start intervention												
Participant follow-up (up to 12 months)												
Data management and data analysis												
Dissemination: report writing; stakeholder meetings												

18 Budget

Items	**Total (KES)**
Personnel – salaries and salary disbursements	16,200,000
Other direct research cost	1,145,000
Local travel	960,000
Participant compensation	1,032,000
Supplies and equipment	1,715,000
Contingency (5%)	1,052,000
TOTAL	22,104,000

Funding has been obtained by the Burnet Institute from the National Health and Medical Research Council (NHMRC), Australia (GNT1087006 and GNT1090805)

19 Annexes

Information and consent forms

1. Patient information and consent form for cRCT
2. Patient information and consent form for qualitative interviews (women)
3. Patient information and consent form for qualitative interviews (male partners)
4. Invitation letter for male partners
5. Patient information and consent form for Eyenaemia mobile application

Data collection tools

6. Structured questionnaire (month 0)
7. Structured questionnaire (month 6)
8. Structured questionnaire (month 12)
9. Qualitative interview guide for women in SRH arm who did not become pregnant during the trial
10. Qualitative interview guide for women in SRH arm who become pregnant during the trial
11. Qualitative interview guide for boyfriend / husband of women in SRH arm

Screening and enrolment tools

12. Pre-screening form
13. Referral card
14. Clinical assessment form
15. Eligibility form

Clinical test forms

16. Point-of-care test result form
17. Laboratory test result form

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___4-6_____
	6b	Explanation for choice of comparators	___3,6_____
Objectives	7	Specific objectives or hypotheses	___7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____9,10_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___10_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____8,9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____N/A_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____N/A_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____N/A_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___13_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____10-12_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____11_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____10-11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____10-11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__11-12_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___N/A_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____12, _____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____13_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___13_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____13_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____N/A_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__14_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___N/A_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___13_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___13_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13-14_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___16_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____16_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___N/A_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____N/A_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____11-12_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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WHISPER or SHOUT study: Protocol of a cluster-randomised controlled trial assessing mHealth sexual reproductive health and nutrition interventions among female sex workers in Mombasa, Kenya

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WHISPER or SHOUT study: Protocol of a cluster-randomised controlled trial assessing mHealth sexual reproductive health and nutrition interventions among female sex workers in Mombasa, Kenya

Frances H. Ampt*[1,2], Collins Mudogo*[3], Peter Gichangi[3,4,7], Megan S.C. Lim[1,2], Griffins Manguro[3], Matthew Chersich[5], Walter Jaoko[4], Marleen Temmerman[3,6,7], Marilyn Laini[3], Liz Comrie-Thomson[1], Mark Stoové[1], Paul A. Agius[1,2,8], Margaret Hellard[1], Kelly L'Engle[9], Stanley Luchters[1,2,7]

Affiliations:
1. Burnet Institute, Australia
2. Department of Epidemiology and Preventive Medicine, Monash University, Australia
3. International Centre for Reproductive Health (ICRH), Kenya
4. University of Nairobi, Kenya
5. Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, South Africa
6. Aga Khan University, Kenya
7. International Centre for Reproductive Health (ICRH), Department of Obstetrics and Gynaecology, Ghent University, Belgium
8. Judith Lumley Centre, La Trobe University, Australia
9. University of San Francisco, USA

* these authors contributed equally to the manuscript.

Corresponding author: Associate Professor Stanley Luchters
Stanley.luchters@burnet.edu.au

Abstract

Introduction: New interventions are required to reduce unintended pregnancies among female sex workers (FSWs) in low- and middle-income countries, and to improve their nutritional health. Given sex workers' high mobile phone usage, repeated exposure to SMS messages could address individual and interpersonal barriers to contraceptive uptake and better nutrition.

Methods: In this two-arm cluster randomised trial, each arm constitutes an equal-attention control group for the other. SMS messages were developed systematically, participatory and theory-driven, and cover either sexual and reproductive health (WHISPER) or nutrition (SHOUT). Messages are sent to participants 2–3 times/week for 12 months, and include fact-based and motivational content as well as role model stories. Participants can send reply texts to obtain additional information. Sex work venues (clusters) in Mombasa, Kenya, were randomly sampled with a probability proportionate to venue size. Up to 10 women were recruited from each venue, to enrol 860 women. FSWs aged 16–35 years, who owned a mobile phone and were not pregnant at enrolment were eligible. Structured questionnaires, pregnancy tests, HIV and syphilis rapid tests, and full blood counts were performed at enrolment, with subsequent visits at six and 12 months.

Analysis: The primary outcomes of WHISPER and SHOUT are unintended pregnancy incidence and prevalence of anaemia at 12 months respectively. Each will be compared between study groups using discrete-time survival analysis.

Potential limitations: Contamination may occur if participants discuss their intervention with those in the other trial arm. This is mitigated by cluster recruitment and only sampling a small proportion of sex work venues from the sampling frame.

Conclusions: The design allows for the simultaneous testing of two independent mHealth interventions for which messaging frequency and study procedures are identical. This trial may guide future mHealth initiatives and provide methodological insights into use of reciprocal control groups.

TRIAL REGISTRATION: ACTRN12616000852459

STRENGTHS AND LIMITATIONS OF TRIAL DESIGN

Strengths of the study include:

1. Use of a cluster-RCT with reciprocal controls allows for the simultaneous testing of two mHealth interventions, for which message frequency and study processes are identical; only the content of the messages differs.
2. Testing two independent hypotheses simultaneously is efficient, using considerably fewer resources than needed for two independent trials.
3. The design mitigates biases from unequal attention in trial groups (i.e., the groups have comparable interaction with the study team), positive expectations and non-blinding.

Important limitations of the study:

1. Contamination may occur if women receiving SRH messages share them or discuss their content with women in the nutrition arm, and vice versa. Contamination would diminish the ability to detect a difference in effectiveness between the two groups. Cluster-based intervention allocation has been used to reduce the potential for contamination between individuals; however, FSWs often work from multiple venues, so may come in contact with participants from other clusters. In addition, we have recruited only a small proportion of sex workers across a large geographic area (up to 106 of 760 hot spots, and 860 of an estimated 8,516 FSWs), which diminishes the chances of interaction between trial arms. Lastly, we will attempt to measure contamination by asking about message sharing in the questionnaire.
2. A further limitation of this design is that the outcomes of the interventions may interact. While the two health domains were chosen due to the minimal overlap between behaviours, there are some plausible points of influence between the arms. For example, higher rates of pregnancy in the nutrition arm may lower haemoglobin and iron levels in these women. More generally, those receiving messages on one aspect of health may improve their health behaviours across multiple health domains, potentially diluting the effect measures of the comparison between the study arms.
3. It is also important to note that the SRH intervention aims to increase demand for contraceptives, and that translating demand into raised coverage may be limited by deficiencies in the health system (supply-side issues). These could include commodity stock-outs, insufficient choice of methods offered to women, and discriminatory treatment of FSWs by health workers. Supply-side issues may also influence outcomes in the nutrition group, for example, if a limited range of foods is available in the household, or area more generally.

4. Although nutrition messages may alter knowledge and attitudes, women's socio-economic conditions may preclude a change in diet and thus in nutritional markers such as haemoglobin.
5. The use of both push and pull technologies is a novel and potentially powerful approach, but their simultaneous use may make it difficult to determine the size of their independent effects. We will perform a dose-response sub-analysis to examining whether differential exposure to messages (pull or push) is associated with the trial outcomes.

INTRODUCTION

Female sex work

Despite sex work being very common in sub-Saharan Africa, with one in 20 women estimated to have exchanged sex for money, goods or other favours,[1] it remains a highly stigmatised and mostly criminalised practice, including in Kenya.[1 2] The hostile politico-legal and social environment limits sex workers' access to health services, especially for sexual and reproductive health (SRH), and for preventing and treating HIV and other sexually transmitted infections (STIs).[3] Strategies such as providing peer education and outreach services are often unable to overcome the myriad structural, personal and financial challenges that female sex workers (FSWs) face.[4] This complex situation calls for new interventions that complement the current package of services and improve health and social outcomes for sex workers.

Unintended pregnancies among female sex workers

In many low-income countries, increased provision of low-cost contraceptive methods has raised contraception coverage in the general population,[5 6] but such gains remain inequitably distributed within countries,[7] and they have not translated into improvements for FSWs.[8] This is due to a combination of *individual* barriers to uptake, such as side effects of some contraceptive methods that impact sex work, and myths and misconceptions about particular methods;[9 10] *interpersonal* barriers, including peer norms and pressure from partners not to use contraception;[8] and *structural* barriers, such as stigmatising treatment of FSWs in the health system.[11 12] Most programs established to improve the health of FSWs focus primarily on HIV and other STIs, and overlook FSWs' broader reproductive needs.[8 13 14] A systematic review of SRH projects aimed at FSWs in Africa found that few provided pregnancy testing or contraceptive services other than condoms, and few specifically promoted dual method use (the concurrent use of condoms and another effective contraceptive method).[15]

Available data indicate that use of contraception other than condoms by FSWs in sub-Saharan Africa is variable, but generally low, ranging from around 15% to 50%.[8]

[16-18] Dual method use is rarely measured, but estimated at 10% in one study in Mombasa, Kenya.[8] The most popular modern method, injectable progestin,[19] is prone to discontinuation and contraceptive failure due to incorrect use.[20 21] In contrast, highly effective and low maintenance long-acting reversible contraceptives (LARCs; intrauterine devices and subdermal implants) are under-utilised, with only 7% of a sample of FSWs in Mombasa reporting ever using these methods.[8]

While few studies have aimed specifically to measure unintended pregnancy among FSWs, HIV prevention studies among FSWs have reported unexpectedly high rates of pregnancy, with 12-month cumulative incidence of 24% in Kenya,[8] 23% in Madagascar,[17] 27% in Rwanda[22] and 23% in the Caribbean.[23] Unintended pregnancy exposes women to significant health and social risks, such as unsafe (and often illegal) abortion, high maternal and infant morbidity and mortality for those who continue with the pregnancy,[24] and increased financial dependence on sex work, which in turn increases their risk of HIV, other STIs, violence and repeat pregnancies.

Nutrition and nutritional status among female sex workers

Urban food insecurity is a growing public health problem in sub-Saharan Africa, and disproportionately affects poor populations, who are more exposed to nutritional risks and have less capacity to adopt effective coping strategies.[25] Also, as a result of rapid urbanization in low- and middle-income countries – and associated changes in diet, leading to over-reliance on non-home prepared food that tends to be high in energy, sugar and salt, and low in nutrients – under-nutrition and micronutrient deficiencies are increasingly occurring alongside over-nutrition, overweight and obesity.[25-27] Both under-nutrition and over-nutrition are risk factors for poor health and mortality globally.[28] In women of reproductive age, micronutrient deficiency leads to pregnancy complications and greater child and maternal morbidity and mortality.[29] Anaemia, predominantly caused by iron deficiency, is endemic among women in sub-Saharan Africa; in Kenya, 36% of pregnant women and 25% of non-pregnant women are estimated to be anaemic.[30]

While there are no published data on malnutrition among FSWs in Kenya, lack of physical activity, chaotic lifestyles and poor diet may lead to unhealthy weight gain, while at the same time contributing to their risk of micronutrient deficiency. Equally, food insecurity and hunger have been identified as key push factors for women to initiate and continue sex work.[31 32] In one study of sex workers in the Lagos metropolitan area in Nigeria, 35% of respondents had entered sex work in response to food insecurity.[33]

mHealth interventions

Mobile phones have the potential to effectively engage FSWs, provide information, improve knowledge, and address individual and interpersonal barriers to contraception use and nutritional health. Mobile phone coverage is over 80% in

Kenya,[34] and close to ubiquitous among FSWs, who constitute a large mobile population that relies on mobile phones for maintaining social and business networks (unpublished formative research from Mombasa). mHealth interventions allow for repeated, theory-driven, user-centred and low-cost exposure, which is known to be important for securing behaviour change.[35]

Several systematic reviews have shown that short messaging service (SMS) technology can influence health behaviour.[36-39] There are, however, few randomised controlled trials (RCTs) addressing SRH behaviour through SMS.[40-42] Two trials in Australia demonstrated improvements in health-seeking behaviour and sexual health outcomes, particularly among young women.[41 42] Non-randomised trials and program evaluations have also had positive findings.[43 44] With regards to nutrition, trials in the USA and Iran have demonstrated the efficacy of SMS for changing eating behaviours,[45] and knowledge and attitudes towards iodine consumption[46] respectively. SMS interventions targeting over-nutrition have also been tested,[47-51] some of which were associated with significant weight reduction.[47-49]

Overall, research is failing to keep up with the rapid proliferation of mHealth interventions.[38] Despite the potential gains, there remains a lack of rigorous research on SRH promotion initiatives in LMICs,[52] and within the field of nutrition the lack of rigorous data is even more pronounced. Furthermore, among populations like FSWs from low-resource settings, who tend to have lower health knowledge and fewer resources for obtaining health information, intervention impact may be greater than that observed in high-income countries, but this has yet to be demonstrated empirically.

WHISPER and SHOUT interventions

The Women's Health Intervention using SMS for Preventing Unintended Pregnancy (WHISPER) study was developed in response to the substantial SRH needs of FSWs in Kenya, the potential benefits of increasing demand for family planning among FSWs through mHealth, and the research gaps in this field. If found to be effective, mHealth for SRH could complement and increase the effectiveness of the current service packages provided for sex workers.

Similarly, the need to improve nutrition for women in poor and vulnerable settings, and the paucity of data on FSWs' nutritional health, led to the development of the SMS intervention to improve nutritional Heath OUTcomes (SHOUT). The SHOUT trial will provide important preliminary data on this under-investigated issue, and explore whether mHealth is an effective means of reducing malnutrition and anaemia in this population.

This paper presents the protocol for the WHISPER or SHOUT study. Recruitment and enrolment took place from September 2016 to May 2017, and 12-month data collection is anticipated to finish by June 2018.

METHODS AND ANALYSIS

This is a two-arm cluster RCT, which will examine the effectiveness of parallel interventions, addressing SRH and nutrition, delivered via mobile phone among FSWs in Mombasa, Kenya. As each intervention addresses a unique set of specific issues, and the mode of delivery and level of exposure is the same, each trial arm serves as a control group for the other.[53 54]

Study objectives and outcomes

The overall aim is to improve the health and wellbeing of FSWs in resource-constrained settings. Specifically, the study will assess the effectiveness of two independent 12-month mobile phone-delivered interventions in improving:

i) SRH outcomes for FSWs receiving the WHISPER intervention, compared to women receiving a nutrition intervention; and

ii) nutritional status for FSWs receiving the SHOUT intervention, compared to women receiving an SRH intervention.

The feasibility and acceptability of the interventions will also be assessed, using a combination of quantitative methods (structured questionnaires at six and 12 months) and qualitative methods (in-depth interviews at 12 months).

WHISPER

The primary study outcome for WHISPER is the incidence of unintended pregnancy over 12 months of follow-up. Unintended pregnancy is defined as pregnancy that is mistimed, unplanned, or unwanted at the time of conception.[55] Women in the study are asked about their pregnancy intentions for the forthcoming six months at enrolment, and at the six and 12-month visits. A psychometrically-validated six-item questionnaire (London Measure of Unintended Pregnancy) will also be used to score pregnancy intention when pregnancy occurs during study follow-up.[56] Pregnancy events are defined as either a positive result on urine pregnancy screening at the six or 12-month visits (or at unscheduled visits at the study clinics, should these occur), or a self-reported pregnancy that occurs between study visits (captured by the follow-up questionnaire).

Secondary outcomes are being measured at baseline and six and 12 months, and include incidence of HIV and syphilis measured by point-of-care testing. Self-reported secondary outcomes, assessed by structured questionnaire, include SRH knowledge, behaviour (prevalence of LARC and dual method use) and service utilisation.

SHOUT

The primary study outcome for SHOUT is the prevalence of anaemia at 12 months of follow-up. This outcome is measured using a certified laboratory-based haematology machine at baseline and 12 months, and is defined as haemoglobin level below

12.0g/dL, consistent with the World Health Organization (WHO) definition).[30] A point-of-care haemoglobinometer will also be used to enable immediate management of anaemia, but the laboratory measure will be used to calculate the primary outcome.

Secondary outcomes include mean haemoglobin (Hb) levels at 12 months, prevalence of malnutrition (measured by body mass index and middle-upper arm circumference (MUAC) at baseline and six and 12 months), and self-reported nutritional knowledge and behaviour (assessed by structured questionnaire at baseline and six and 12 months).

Study intervention

Development of WHISPER or SHOUT study interventions

Changes in attitudes and behaviours are most likely to occur when communication interventions are theory-driven, interactive and follow best practice in design and implementation.[57] Furthermore, sustainable positive behaviour change among individuals and communities occurs as a process, supported by carefully designed interventions, and not as a single event.[58 59]

The WHISPER and SHOUT interventions were therefore developed following a pre-defined protocol and in a systematic and participatory manner, ensuring that the intervention was grounded in evidence, was relevant and acceptable to the study population, and followed a logical process of behaviour change based on staged and social cognitive theoretical approaches.[60] An extensive review of the literature and consideration of health behaviour change theory informed the development of logic models for both study arms (figures 1 and 2), and the subsequent drafting of messages. Participatory and user-centred design and testing of the mobile phone intervention[61-63] was conducted with the target population in four informal consultative meetings, 12 formal workshops and 24 usability testing interviews. FSWs were involved in identifying important issues that affect them, developing messages and role model stories, reviewing and refining the content, and suggesting changes to the intervention architecture.

Structure and delivery of the intervention

Both the SRH and nutrition intervention consist of SMS (text) messages sent to participants two to three times per week for 12 months. The intervention includes the following components:

- ‘push’ texts covering the main content domains, providing simple information, motivational messages and strategies to prompt action;
- ‘role model stories’ about FSWs modelling healthy social norms and sent in 4–5 instalments in one month (alternating months with stand-alone messages); and

- a 'pull' or on-demand menu that participants can access by texting into the system to obtain more information on high-priority topics and local services.

The intervention is being delivered by the VOTO mobile (https://www.votomobile.org/) online platform. All messages are loaded onto the system in a pre-determined order and sent automatically to each cluster of participants at the scheduled time (calculated from each cluster's start date). Participants are able to text assigned codes at any time during the study to access the pull messages, with SMS costs incurred by the study (no charge for participants). Content is only accessible to enrolled participants in the relevant intervention group, so that those in the nutrition arm cannot directly access SRH messages, and vice versa.

Table 1 presents a summary of the structure of the interventions, showing that they are essentially equivalent in all structural components except the on-demand system. This discrepancy is due to additional pull messages in WHISPER that provide information about SRH services, allowing participants to link in with local sex worker-sensitive providers. This was deemed important on ethical grounds given the sensitive content of the WHISPER intervention, and because promotion of contraception can only impact pregnancy rates if delivered alongside accessible services that provide the methods in question. In contrast, the promotion of healthy eating does not require an intermediate service utilisation step to result in improved nutritional outcomes. Furthermore, low-cost or free nutrition services are not widely available in Mombasa, and screening asymptomatic non-pregnant women for anaemia is rarely practised, so we were unable to reliably list relevant services for SHOUT.

Table 1: Number, length and timing of messages for each study arm

Message type	Number of messages	Length	Timing
Push messages	82 (both arms)	Up to 160 characters (1 SMS 'screen')[1]	3 per week (Monday, Wednesday and Saturday mornings) during months 1, 3, 5, 7, 9, 11, 13[2]
Interview reminders and study information (push messages)	7 (both arms)	160–480 characters (1–3 screens)	Months 6, 7, 13
Role model stories (push messages)	26 (SRH); 27 (nutrition) (covering 6 stories for each arm)	160–640 characters (1–4 screens) per message	2 per week (sent Monday and Friday mornings) during months 2, 4, 6, 8, 10, 12
'Alerts': push messages linking participants to the pull system	19 (SRH); 18 (nutrition)	160–320 characters (1–2 screens)	
Pull (on-demand) messages	80 (SRH); 49 (nutrition)	160–640 characters (1–4 screens)	User determined

[1] Messages are charged per 160 characters (1 screen). Messages longer than this will appear as one long SMS on most phones, but may be split into multiple messages on older phones.

[2] There are 13 blocks of four weeks each, making up 12 calendar months in total.

Setting and participants

Eligible women were recruited from mapped sex work venues by well-established peer outreach workers. Sex work venues consist of fixed-site businesses including nightclubs, bars, brothels and hotels, as well as public spaces such as street corners and beaches, where sex is known to be bought and sold. The study is being conducted in two areas of Mombasa, a major economic centre in Kenya and East Africa, with busy port, rail and industrial enterprises. The local implementing partner, International Centre for Reproductive Health (ICRH; a WHO Collaborating Centre for Reproductive Health in Mombasa) has a research track record in the area dating back to 2002, including many trials and other prospective intervention studies with FSWs[64-66] and numerous non-interventional studies.[67-70]

Inclusion and exclusion criteria

To be eligible for participation, women had to: 1) be aged 16 to 35 years; 2) report having engaged in sex work (received money in exchange for sex) at the site of recruitment in the last six months; 3) not be pregnant or planning pregnancy within 12 months; 4) reside, within the study area for the duration of the study; 5) have a personal mobile phone with Safaricom or Airtel subscription, and be willing to provide the phone number to the researchers to receive the intervention messages; 6) report being SMS literate (i.e., able to read text messages in English); 7) be willing to return for follow-up after six and 12 months; 8) be willing to provide contact information (e.g. home address) to enable contact or a visit from a member of the research team in the community to remind them to attend follow-up visits; and 9) be able and willing to give written informed consent for enrolment in the study. Exclusion criteria included participation in another mHealth intervention study or in the formative research for this study, and having a medical or non-medical condition detected through screening that hinders study participation, as confirmed by the local Principal Investigator.

Randomisation and sampling strategy

ICRH and collaborators conducted a two-stage geographic mapping and enumeration exercise of FSWs in 2014, estimating that 11,777 (range 9,265–14,290) FSWs operate from 1053 venues across four sub-counties of Mombasa County.[62] We are recruiting FSW from two of these areas: Changamwe (where an estimated 3,435 FSWs work from 285 venues) and Kisauni (where an estimated 5,081 FSWs work from 475 venues).[62]

A two-stage sampling process was adopted, drawing on this sampling frame. At the first stage, FSW venues were selected with a probability proportionate to the enumerated size of the sex worker population at the venue, and randomised to

either the WHISPER or SHOUT arm. Each venue was considered to be a separate cluster. At the second stage, 10 FSWs were consecutively selected from each venue, based on an estimated mean cluster size of 11.[62] At venues where less than 10 FSWs were active, all FSWs from the selected venue were invited to participate in the study. Sampling of FSW venues continued until the required sample size was achieved.

Cluster randomisation (allocation of each cluster to either WHISPER or SHOUT) was done centrally by the statistician and prior to recruitment commencing, involving an equal number of clusters in both arms. The participants and study team were blinded to allocation until after cluster enrolment was completed and all baseline questionnaires had been administered for that cluster.

Overall, our approach aimed for optimal (as random as possible) sampling from the FSW population, while minimising the potential intervention dilution effects of message sharing that might occur with individual-level randomisation.

Recruitment and enrolment

Community mobilisers and peer educators employed by the study applied minimum pre-screening criteria at the site of recruitment to identify potential study participants. Potentially eligible women received a card with a unique, anonymous *referral card number* (made up of cluster number and sequential participant number for that cluster). They were asked to attend the nearest study clinic for full eligibility screening, consenting and enrolment within the next three days. The study clinics are open five days a week and are embedded in existing facilities: an ICRH-run sex-worker drop-in centre in Kisauni and a municipal community health centre in Changamwe. The number of sex workers approached and referral cards disbursed at each cluster was documented, as well as reasons for ineligibility at pre-screening. Volunteers had to bring their referral card number with them to undergo the screening process to ensure that only volunteers selected by the random sampling process were enrolled. Women who consented to participate and successfully completed full screening had their study identification number assigned and were then formally enrolled.

Data collection

Study visits were conducted at enrolment and will be repeated after six and 12 months at the study clinics. All study staff, including clinicians, research assistants, community mobilisers and peer educators, were trained in the study procedures during a five-day workshop and undertake additional targeted sessions where required.

Enrolment procedures include collecting informed consent, administering the baseline questionnaire, and performing clinical examination, urine pregnancy test, point-of-care blood tests for HIV, syphilis, and Hb level, and venepuncture for full

blood count (haemogram: Hb, haematocrit, mean cell volume and white blood count). Follow-up assessments are presented in Table 2.

Table 2: Schedule of assessments for the WHISPER or SHOUT trial

Assessments	Month 0	Month 6	Month 12
Structured questionnaire	✔	✔	✔
Clinical examination	✔	✔	✔
Urine pregnancy testing	✔	✔	✔
Point-of-care HIV and syphilis testing (including pre- and post-test counselling)	✔	✔	✔
Hb measured by haemoglobinometer	✔		✔
Full blood count	✔		✔
In-depth interviews (subgroup of participants from SRH arm)			✔

Questionnaires were developed in English and translated into Swahili, and were based on previously validated measurement tools wherever possible. The questionnaire captures detailed socio-demographic information including education, literacy, employment, income, family and living circumstances, health and illness, and sex work history. SRH enquiries cover previous pregnancy(ies); six-month pregnancy intention; contraception and condom use (including dual protection); reasons for discontinuation or non-use of contraception; contraceptive self-efficacy; sexual and reproductive health seeking and service utilisation; sexual risk behaviours; SRH knowledge and attitudes; and relationship control and joint-decision-making with non-paying emotional partners. Participants are asked about whether they have recent STI-related symptoms, which are classified and treated as per syndromic STI guidelines.[71] Nutrition questions gather data on nutrition-related health seeking and service utilisation; food and hygiene-related knowledge and behaviours; dietary intake and preparation; and food purchasing.

Clinical examination is performed by study clinicians, and includes STI syndromic management and anthropometric measurements to assess nutritional status (i.e. weight, height, waist circumference, hip circumference and MUAC).

The results of rapid diagnostic tests are communicated to the participants at the time of the visit. Participants newly diagnosed with HIV are referred for treatment at specialised centres. Those with positive syphilis rapid test are treated with benzathine penicillin at the study visit. Participants with anaemia receive one month of iron and folic acid supplementation and a referral to a health facility for follow-up.

Following enrolment, each participant was registered in the VOTO online platform. No identifying details apart from mobile phone number were entered. Intervention allocation was performed by data management staff independent of the study team, and occurred after enrolment was completed for each cluster. The intervention commenced simultaneously for all participants of one cluster in the week following completed cluster-level enrolment.

DATA ANALYSES

Analysis of primary endpoints

Primary analysis for WHISPER and SHOUT will compare the primary endpoints (unintended pregnancy incidence and anaemia prevalence respectively) between groups at 12 months. The data analysis team will be blinded to the allocation of participants. Given the interval-censored nature of unintended pregnancy incidence, discrete-time survival models using generalised linear modelling will be used to compare unintended pregnancy incidence between the two trial arms. Comparison of differences in prevalence of anaemia between study arms will be undertaken using multi-level generalised linear modelling.

These analyses will, where appropriate, provide estimates with robust standard errors for FSW venue clustering. Standardised probability weighting will be applied in population-averaged analyses to account for any sampling bias where achieved sample cluster sizes vary. Also, where randomisation is not effective in removing allocation bias, adjusted models will be specified. In all analyses, associations will be considered statistically significant at the 5% level.

Sample size

The sample size was calculated to obtain sufficient power to examine the effects of the SRH intervention. Based on a 12-month incidence of unintended pregnancy of 24% in the control group (data from previous research in the study population),[8] enrolment of 860 participants from a minimum of 86 FSW venues would enable detection of a relative reduction in annual unintended pregnancy incidence of 37% (hazard risk=0.63), at 80% power and 5% significance level. This estimate was adjusted for an expected 10% attrition rate (based on previous experience with this population[8]) and an estimated inflation in standard error due to cluster randomisation (design effect=1.18; estimated intra-cluster correlation coefficient (ICC)=0.02, with a cluster size of 10).[72]

Sample size could not be reliably calculated for the SHOUT trial as estimates of anaemia in the local sex work population are not available. However, if we assume a prevalence of 25% (as per the national estimate for non-pregnant women[30]), the calculated sample size of 860 would allow for detection of an approximate 42% reduction in odds of anaemia prevalence, with inflation in standard error and attrition rate adjustments applied as above.

ETHICS AND DISSEMINATION

Written informed consent has been obtained from every study participant. Women aged 16 and 17 years are considered mature minors, and able to consent without involving parents and guardians, due to the sensitive nature of the subject matter. Informed consent forms are available in both Kiswahili and English, and describe the

purpose of the study, the procedures to be followed, and the risks and benefits of participation. Most importantly, we are aware of the risk that others seeing the messages may infer that the participant is a sex worker. It is important to mitigate this risk of unintentional disclosure of sex work status and consequent stigma or other adverse events for participants.[73] Participants have been counselled about the need for care to be taken to ensure that others do not have access to their phones. The study team also asks that participants report instances of unintentional disclosure. Such reporting allows us to provide support to the women concerned and, through understanding the events surrounding the case, try to find ways to avoid future occurrences.

Ethical approvals have been obtained for protocol version 1.2, dated 22 August 2016 from the Monash University Human Research Ethics Committee (MUHREC - CF16/1552 - 2016000812) and the Kenyatta National Hospital, University of Nairobi Ethics and Research Committee (KNH-UoN ERC – KNH-ERC/RR/493).

Several dissemination activities are planned, including to health workers and the district office, Kenyan policymakers, at local and international conferences, and in academic publications.

Potential impact and significance

The WHISPER study responds to the pressing need for effective and evidence-informed interventions to prevent unintended pregnancies among vulnerable women in resource-constrained settings. Persistent unmet need for family planning contributed to inadequate progress towards reducing child mortality and improving maternal health (Millennium Development Goals 4 and 5), and to the need for the 2010 Global Strategy for Women's and Children's Health.[7] The ability to decide on the number and timing of children, free from coercion and violence, is a fundamental human right. During the 2012 London Summit on Family Planning,[74] the Kenyan Government committed to increasing funding and contraception coverage by 2015. Despite this supply-side commitment, questions remain about the optimum mechanism to increase demand, particularly among marginalised populations. The WHISPER trial will assess an innovative, sustainable and scalable approach to address some of these gaps.

Study outcomes will be used to inform future policies and public health interventions aimed at increasing uptake of family planning, as well as other SRH services, among vulnerable populations in a range of similar settings, particularly in LMICs. The rigorous research design and extensive local experience of our team will support advocacy and guide mobile technology services for health promotion as outlined in the 2010 Kenyan Government's Family Planning Guidelines.[75] If found to be effective, this intervention could be sustainably scaled up across East Africa.

With regards to nutritional health, there are renewed efforts to design and implement action-oriented research, but the role of mHealth in these initiatives

remains uncertain.[76] The SHOUT study will go some way towards clarifying whether SMS technology is a useful way of responding to a long-recognised, but poorly characterised and neglected problem. Indeed, if shown to be effective in this trial, mHealth could be incorporated into broader nutrition strategies for FSWs in Africa and elsewhere, and has the potential to be scaled up for use with other women at a population level.

The design mitigates biases from unequal attention in trial groups, positive expectations and non-blinding.[53 54] The innovative approach described herein has never been used to prevent unintended pregnancies or improve nutrition among key risk populations in LMICs. A similar methodology in which the effects of SRH text messages were compared to a control SMS intervention was adopted in Australia with a sun safety control group,[41] and in the USA with a nutrition control group,[44] although the latter did not measure nutrition outcomes, unlike our trial. This trial will thus set standards for the mHealth field in LMICs, for both interventions and trial methodology. Lessons learnt about optimising SMS technology for both WHISPER and SHOUT could have considerable impact in Kenya, and similar countries, for a range of health priorities outside of those examined here.[69]

In conclusion, FSWs constitute a large, vulnerable, hard-to-reach population that could be amenable to mHealth interventions given their high mobile phone coverage and utilisation. FSWs are at considerable risk of unintended pregnancies, and could benefit markedly from interventions that increase uptake of contraception, with an emphasis on long-acting reversible technologies and dual method use. Similarly, the nutrition arm of the trial responds to the paucity of quality data on rates of malnutrition among sex workers and of effective interventions to improve their nutritional status and metabolic health.

A cluster RCT with an equal-attention control and objective biological primary endpoints (unintended pregnancy and anaemia) is the most robust study design to test the effectiveness of the planned interventions. It is anticipated that the trial will contribute important evidence to mHealth initiatives among vulnerable populations and provide useful methodological insights into the use of reciprocal control groups within such trials.

Author declarations

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Author contributions

The following authors were investigators on the trial from the outset: Frances Ampt, Collins Mudogo, Peter Gichangi, Megan Lim, Matthew Chersich, Walter Jaoko, Marleen Temmerman, Marilyn Laini, Liz Comrie-Thomson, Mark Stoové, Paul A. Agius, Margaret Hellard, Kelly L'Engle, Stanley Luchters. Griffins Manguro more recently joined the trial site in Kenya, leading work in that site. The paper draws from the trial protocol, which was written collectively, under the leadership of the Principal Investigator Stanley Luchters. All authors read and approved the final version of the paper.

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Competing Interests

None declared

Ethics approvals

Monash University (MUHREC)

Kenyatta National Hospital Ethics and research committee

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

Data presented in this paper are available from the corresponding author on request.

Figures

Figure 1: Logic model for the sexual and reproductive health intervention (WHISPER)

Figure 2: Logic model for the nutrition intervention (SHOUT)

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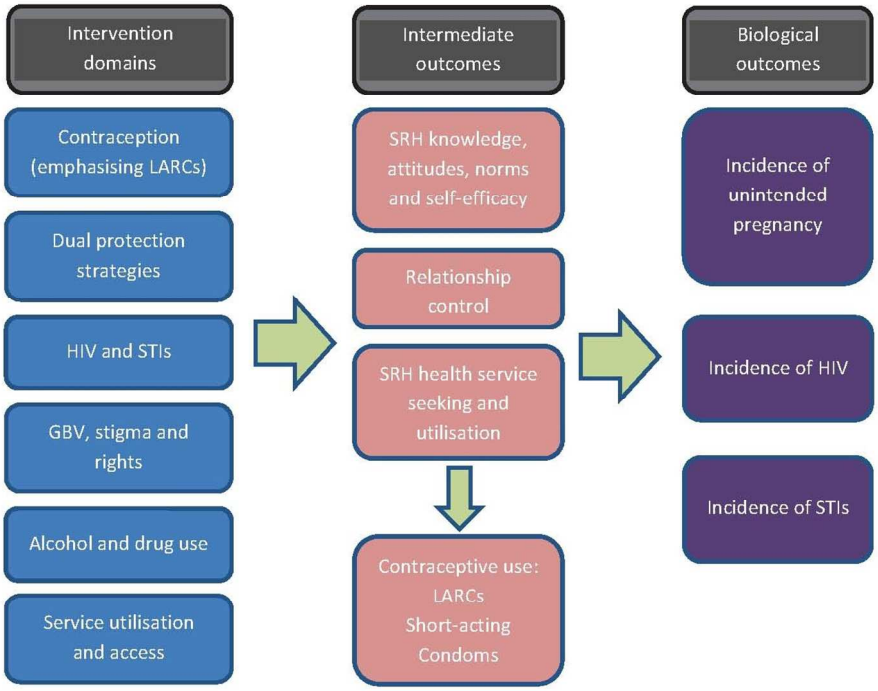

Figure 1. Logic model for the sexual and reproductive health intervention (WHISPER)

122x86mm (300 x 300 DPI)

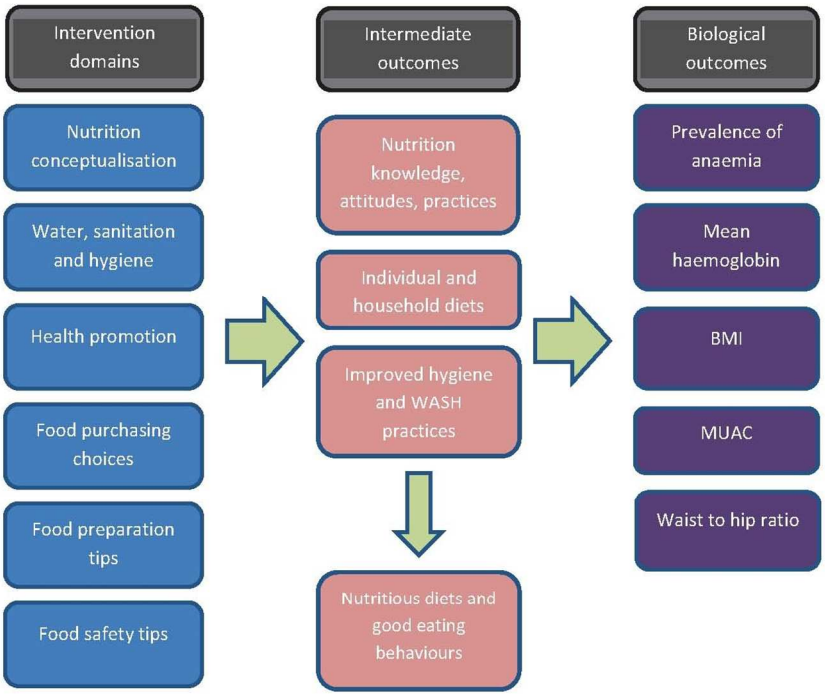

Figure 2. Logic model for the nutrition intervention (SHOUT)

127x90mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___4-6_____
	6b	Explanation for choice of comparators	___3,6_____
Objectives	7	Specific objectives or hypotheses	___7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____9,10_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___10_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____8,9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____N/A_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____N/A_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____N/A_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___13_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____10-12_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____11_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____10-11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____10-11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__11-12_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___N/A_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____12, _____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____13_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___13_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____13_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____N/A_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__14_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___N/A_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___13_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___13_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13-14_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___16_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____16_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___N/A_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____N/A_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____11-12_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.