Title: Implementation and Evaluation of a Large-scale Postpartum Family Planning Program in Rwanda

Date: Aug 14th 2023

NCT#: NCT05056545

PROTOCOL TITLE: Implementation and evaluation of a large-scale postpartum family planning program in Rwanda

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VERSION: v4.0 14Aug23

FUNDING SOURCE: National Institutes of Health

REVISION HISTORY

Revision #	Version Date	Summary of Changes
1 (version 2.0)	14Apr22	• Reduced the number of intervention facilities from 12 to 10 • Clarified that a subset of women will be selected for an additional follow-up survey 9 months post PPFP provision • Replaced with figure which indicates when various post-partum contraceptive methods may be administered postpartum with an updated version • Removed facility staffing/volume estimates (out of date) • Clarify that interim analyses will be conducted at the midpoint of year 3 (not year 2 of the overall project, which was meant to refer to year 2 after intervention implementation) • Added that collection and monitoring unanticipated problems, in addition to (S)AEs, are included in the DSMP

		• In lieu of providing the details contained in the DSMP, the DSMP is submitted to the IRB for review • Noted in the timeline that facility needs assessments will take place throughout the study • Clarified that PPIUD follow-up visits will take place 4-6 weeks after insertion to correspond with their next IV visit. • Assessment for client satisfaction has been removed. • Under section 10: "Inclusion and Exclusion criteria" The Inclusion criteria has been clarified: Pregnant women or Postpartum women of any age will not be excluded

2 (Version 3.0)	13Feb23	• Reduced 5 pilot facilities to 4 pilot facilities
		• Revised the total estimated number of women and men reached with PPFP promotions reached from >21,000 to >26,000.
		• Revised the reimbursement strategy accordingly:
		  ○ Facilities participating in this study will receive monthly communication fees.
		  ○ Providers participating in this study will receive per diem for their participation in PPFP trainings including refresher trainings.
		  ○ Women who receive a PPFP method will not be compensated, nor will they incur additional expenses for participating in the program. PPFP follow-up visits will be scheduled during regular clinic follow-up (e.g., infant vaccination visits) and management of side-effects will be covered by insurance (mutuelle), which covers >90% of women. Provision of care for uninsured women will be paid for by the study.

3 (Version 4.0)	14Aug23	• We have added detail to the statistical analysis plan to reflect that the primary analysis will compare facility-level data pre- versus post-intervention. • We will conduct fidelity assessments at roughly 6 months after intervention initiation. The 2 month assessment has been removed since it did not allow enough time to establish the intervention and assess its implementation.

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1. Study Summary

Study Title	Implementation and evaluation of a large-scale postpartum family planning program in Rwanda
Study Design	Type 2 effectiveness-implementation hybrid cluster randomized controlled trial
Primary Objective	To evaluate the effectiveness of different demand creation strategies and to test the hypothesis that the post-partum family planning intervention ('C4') is adaptable to largescale implementation, cost-effective, and sustainable
Secondary Objective(s)	Not applicable
Research Intervention(s)/Interactions	Provision of post-partum family planning methods
Study Population	Pregnant women and women seeking antenatal care, labor and delivery services, or infant vaccination services in government health facilities in Kigali, Rwanda
Sample Size (randomized intervention facilities only)	**Training**: 81 government facility PPFP promoters 56 community health worker promoters 65 government facility PPFP providers 30 Happy Client promoters **Service delivery:** 10,553 women (PPFP counseling) 3060 women (PPIUD insertions) 1161 women (PP implant insertions)
Study Duration for individual participants	Maximum of 54 weeks (40 weeks gestation plus 14 weeks postpartum). A subset of women will be selected for an additional follow-up survey 9 months post PPFP provision (maximum study duration 54 weeks + 9 months).
Study Specific Abbreviations/ Definitions	PP: post-partum PPFP: post-partum family planning PPIUD: post-partum intrauterine device IUD: intrauterine device C4: The post-partum family planning intervention LARC: long-acting reversible contraception CHW: community health worker ANC: antenatal care L&D: labor and delivery IV: infant vaccination

	MOH: Ministry of Health PI: Principal investigator PID: pelvic inflammatory disease CAB: community advisory board DSMB: data safety monitoring board AE: adverse event SAE: sever adverse event OHRP: Office for Human Research Protections IRB: Institutional Review Board
Funding Source (if any)	National Institutes of Health

2. Objectives

Aim 1. Implement C4 in 14 high-volume health facilities (4 pilot facilities, 10 intervention facilities). Guided by the Consolidated Framework for Implementation Research, we will assess facility organizational readiness prior to implementation. No PPFP activities are currently taking place in these facilities. We will implement C4 in a clinic randomized step wedge design. We expect to deliver C4 promotional counseling to over 26,000 pregnant or postpartum women and men.

Aim 2. Evaluate C4 effectiveness and implementation. The RE-AIM framework will guide outcome evaluation. We hypothesize that C4 will significantly increase the number of stakeholders engaged, PPFP providers and promoters, couples/clients receiving information about PPFP (reach), and LARC uptake (effectiveness) comparing intervention versus standard of care. We expect PPFP side-effects will be rare. The independent effectiveness of each demand creation strategy on LARC uptake will be estimated. We assess measures of C4 adoption, implementation, and maintenance at the patient-, provider- and stakeholder-level to assess C4 sustainability.

Aim 3. Evaluate C4 cost-effectiveness and cost-utility. We employ standard methods to estimate the costs and incremental cost-effectiveness and cost-utility of C4 relative to standard of care from the societal perspective. The cost-effectiveness of each demand creation strategy will be estimated. We hypothesize that C4 will be cost-saving relative to standard of care. A Costed Implementation Plan will be developed to guide Rwandan MOH decision-making for nationwide roll-out of PPFP services.

3. Background

Uptake and sustainability of PPFP services in Rwanda has remained low. Similar to other countries, the Rwandan DHS estimates that 51% of women have an unmet need for PPFP, higher than unmet need during non-postpartum periods. Also similar to other countries, PP LARC use remains low (among contracepting women, 8% use implants and <1% use the IUD).

To address high unmet need for postpartum family planning (PPFP) in Rwanda, in 2017-2018, we worked closely with the Rwanda Ministry of Health (MOH) to develop and pilot test a theory-based, multi-level intervention targeting PPFP supply and demand in 5 government health facilities in Kigali, the capital. This innovative PPFP intervention is known as 'C4' because it is informed by Clients, Clinic providers, Champions, and Community Health Workers. We developed an educational counseling flipchart which was provided to 9,020 pregnant and postpartum women/couples in health facilities and the surrounding community. Long-acting reversible contraceptives (LARC), the intrauterine device (PPIUD) and implant, are fundamental to PPFP programs. LARCs are highly effective and are the only reversible methods that may be safely used in early postpartum period by breastfeeding women. During our pilot, LARC uptake among postpartum women increased significantly (172% for PP implant, 2,687% for PPIUD), PPFP feasibility and acceptability were high among providers and clients, and side-effects were rare.

While our short pilot was highly impactful in increasing PPFP uptake, much remains unknown: Is C4 scalable without sacrificing quality? Is C4 cost-effective? What demand creation strategies are most effective and cost-effective? Is C4 sustainable? We now propose to use an implementation science framework to test the hypothesis that C4 is adaptable to large-scale implementation, cost-effective, and sustainable. C4 could dramatically reduce unintended pregnancy and abortion and improve birth spacing and maternal and newborn health.

4. Study Endpoints

Primary endpoints

Stakeholders

Clinic directors engaged

Promotions

Nurses trained to promote PPFP

CHWs trained to promote PPFP

Providers at implementation facilities

Providers trained to provide PPFP

Providers certified to provide PPFP

Clients delivering at implementation facilities

Promotions to pregnant or postpartum women/couples

PPIUD insertions

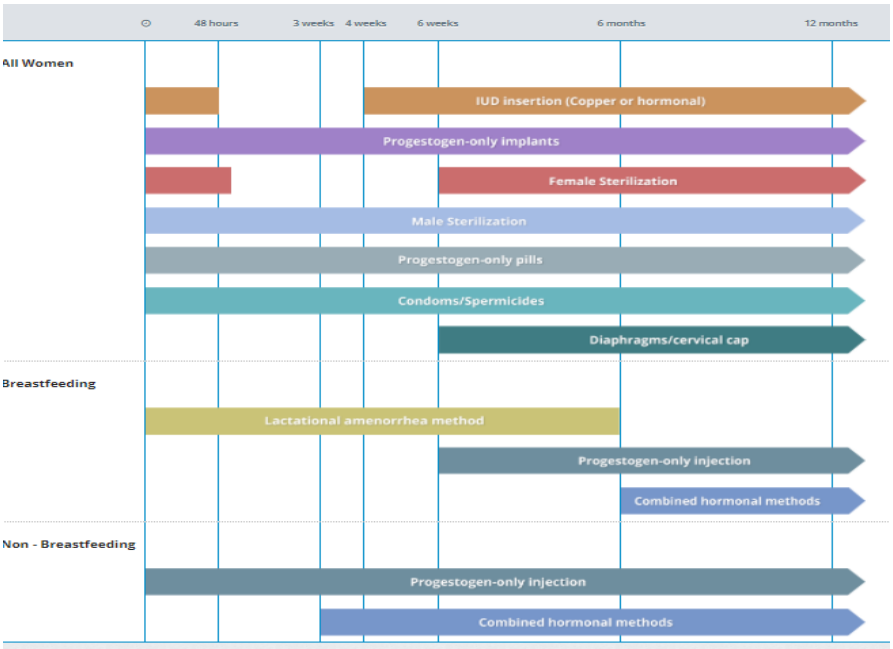
PP implant insertions

Safety endpoints

(Serious) adverse events including: pelvic pain, heavy menstrual bleeding/menorrhagia, dysmenorrhea, infection, perforation of the uterine wall, pelvic inflammatory disease (PID), headaches, irregular periods, nausea, blood clot, minor bleeding, severe bleeding, pain

5. Study Intervention/Investigational Agent

Provision of post-partum family planning methods include: the copper intrauterine device, hormonal implant, tubal ligation, and (after 6 weeks post-partum in breastfeeding women) Depo-Provera and oral contraceptive pills. All of these methods are FDA approved and are provided as current, standard of care in Rwanda. The methods are procured by the Rwandan government and are stored, handled, and administered by trained Rwandan government health facility nurses and doctors. The guide below indicates when various post-partum contraceptive methods may be administered postpartum.



6. Procedures Involved

Organizational readiness checklist. We will conduct facility needs assessments to understand readiness and barriers to C4 implementation. Checklists will measure facility volume and staffing, pharmacy capacity, physical space for C4, current contraception workflows and procurement systems, prior PPFP trainings, PPFP stocks, and any procedures (i.e., PPFP counseling tools or data collection systems) supporting PPFP supply or demand. Each assessment will take 1 hour and will be conducted by trained research staff.

Study design and randomization. We will implement the C4 intervention in 10 facilities in a clinic randomized stepped wedge design. The stepped wedge design will ensure that each facility receives the intervention over time and provides its own standard of care control, limiting secular bias. Facilities are high-volume and have similar client volume and staffing-to-patient ratios. Each clinic will be randomized using the SAS random number generator (SAS Institute v9.4, Cary, NC).

C4 PPFP service delivery training. The 4 C4 pilot facilities (which are not randomized) will serve as sites to train and mentor nurses and midwives working in L&D and family planning at the 10 intervention facilities. The training will include a 2-day didactic session covering PPFP provision, follow-up, use of the C4 counseling flipchart; mock counseling sessions; and PPIUD and PP implant insertion and removal trainings. Pre/post-training tests (adapted from the USAID and Maternal and Child Health Integrated Program Postpartum IUD Training Guide [1]) will consist of 10 true/false questions. Re-training will be offered after one week for trainees who fail to score >80% on post-training evaluation. After passing the didactic training, trainees will be required to correctly insert 5 PPIUDs and 5 PP implants under supervision to be PPFP certified.

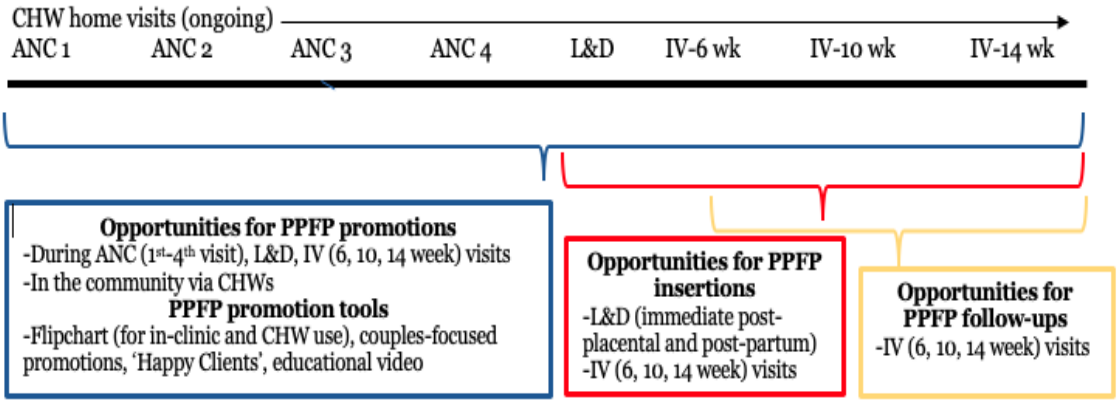


Figure 3. Opportunities for PPFP promotions, insertions, and follow-up visits

The PPIUD insertions must include at least one of each of the following timings (which require different insertion techniques): immediate post-placental, 10 minutes to 48 hours postpartum, and 4-14-weeks post-delivery. We expect to train 65 nurses and midwives to provide PPFP, of whom 70 will be certified.

C4 PPFP demand creation training. Opportunities for PPFP promotions, insertions, and follow-up visits are shown in **Figure 3.** We will train government clinic staff in family planning, ANC, L&D, and IV to promote C4 at the selected facilities. Trainings will be comprised of a 3-hour long didactic session led by trained research staff followed by two supervised counseling sessions. CHWs from the health centers in charge of pregnant women and newborn health will receive a 1-day training on the PPFP flipchart. If interested in PPFP, women will be referred to the facility by their CHW. We expect to train 81 nurses and 56 CHW to promote C4. 'Happy Clients' will be recruited by convenience from women who received promotions and selected PPFP to join a clinic-based PPFP promotions team. We will adapt our Happy Client training materials (used previously in Zambia) to coach them to discuss their own experiences with PPFP and address common concerns (as identified in our formative work and also addressed in the promotional flipchart). Happy Clients will be distributed equally across intervention facilities, affiliated with only one facility, and will be partnered with trained PPFP counselors. We expect to train 30 Happy Clients. Finally, we will create an educational video in which a nurse counselor describes the C4 PPFP flipchart information, visually shows each PPFP option, and men and 'Happy

Clients' give brief testimonies as to their experiences with different PPFP methods. Videos will be shown in the ANC, L&D, and IV waiting areas in intervention facilities.

Follow-up procedures. PPFP follow-up appointments will be scheduled 4-6 weeks after insertion to correspond with their next IV visit. Women will be asked to self-report side-effects including signs of infection and, for PPIUD users, IUD string placement will be checked via bimanual pelvic exam. IUD strings will be trimmed as needed and a pelvic ultrasound given if the strings are not visible during physical exam. Women may decide to discontinue or request a new family planning method of their choice. To increase follow-up, we will provide CHWs with lists of clients in their catchment areas to contact with appointment reminders.

Reimbursements. Facilities participating in this study will receive monthly communication fees and providers will receive per diem for their participation in PPFP trainings including refresher trainings. 'Happy Clients' will be reimbursed for their work.

Data collection. Number of stakeholders engaged and providers trained and certified will be recorded in an Advocacy and Training logbook. CHW counseling activities will be measured on referral slips which will record if a male partner was present. Women/couples receiving one-on-one C4 counseling will have their method of interest, whether a male partner was present, household income, and estimated date of delivery recorded in a PPFP logbook, developed by the study team during the pilot and maintained by government clinic staff. The PPFP logbook will also record PPFP uptake, and, among PP LARC users, provider perception of ease of insertion. During follow-up visits, the PPFP logbook will record PPFP side-effects and method failures. Client age and parity will be abstracted from government Family Planning logbooks.

Implementation. We will conduct a time motion studies wherein The Program Coordinator will follow a random 5% of women/couples offered C4 through their flow of clinical care to record: provider/promoter time, patient wait times, and regular clinical operation disruptions. We expect that <20 min/day will be required by nurses/counselors to deliver the C4 intervention. During these time motions studies, we will also assess implementation fidelity defined using the empirically tested Conceptual Framework for Implementation Fidelity as the proportion of providers adhering to the intervention protocol content as assessed using a standardized checklist of key implementation steps. We expect that the intervention will be implemented per-protocol in 90% of observations. The time motion studies, inclusive of fidelity assessments, will be conducted roughly 6 months months after implementation with re-training as necessary.

Implementation support and trial safety. Nurses/counselors will receive clinical and counseling support from already certified PPFP providers. In the first month of C4 implementation at each facility, the Study Coordinator and two national PPFP trainers involved in our pilot will have daily supervisory contact with the providers to troubleshoot any study or clinical questions; this support will be phased into an 'on call' system for the team to address questions as they arise throughout the trial. We will consult co-I Haddad and local ObGyns as needed for clinical consults. PPFP side-effects will occur during the trial. Serious side-effects will result in a referral for specialist care per current standard of care. All clinical care including management of side-

effects will be provided by government facility personnel at health centers as part of usual care at no cost to the patient or health facility (*see Human Subjects*). An Independent Data Safety and Monitoring Board will monitor safety and women experiencing any serious adverse events will be followed according to the Emory and Rwanda Institutional Review Board-approved site protocol. Interim analyses and stopping rules are described below. We will adapt case report forms from our previous experience with family planning trials and record all clinical queries, responses from the investigative team, and develop subsequent management plans.

Overview of C4 cost-effectiveness and cost-utility. We will employ standard methods of cost analyses as recommended by the Second U.S. Panel on Cost-effectiveness in Health and Medicine to conduct an economic evaluation from the societal perspective (the health care sector costs plus the costs to the participant for participating in the program) to estimate the cost and cost-effectiveness of the intervention relative to control. We will create a Costed Implementation Plan to guide MOH decision-making.

National Costed Implementation Plan. We will create a Costed Implementation Plan following the Family Planning 2020 Costed Implementation Plan Resource Kit https://www.familyplanning2020.org/cip. The Costed Implementation Plan Resource Kit features tools for developing and executing a robust, actionable and resourced family planning strategy. Specifically, the kit includes guidance documents and tools necessary to go through the CIP process. The Resource Kit provides best-practice guidance based on the hands-on experience of governments, donors and technical assistance providers in creating and implementing Costed Implementation Plans. Our team previously developed National Costed Implementation Plans for Couples' HIV testing for Zambia and Botswana at the request of their respective MOHs, and the PPFP Costed Implementation Plan will be disseminated to the Rwandan MOH.

7. Data and Specimen Banking

Not applicable

8. Sharing of Results with Participants

The results of this study will not be shared with individual study participants.

All incidental findings (from any needed pelvic or ultrasound exam) will be shared with participants and their government health facility provider so that standard care may be provided by the health facility.

9. Study Timelines

- Women will participate for a maximum of 54 weeks (40 weeks gestation plus 14 weeks postpartum). A subset of women will be selected for an additional follow-up

survey 9 months post PPFP provision (maximum study duration 54 weeks + 9 months).

- Enrollment will proceed over 3 years of the study (years 2-4)
- The study will be completed in 5 years

Overall timeline of study activities by year (Y) (in 6-month intervals):

Aim	Study Activity	Y1-1	Y1-2	Y2-1	Y2-2	Y3-1	Y3-2	Y4-1	Y4-2	Y5-1	Y5-2
1	Protocol development and IRB approvals	X									
	Facility needs assessments		X	X	X	X	X	X			
	Implement C4 in a randomized step wedge design (*see table below*) and collect effectiveness and implementation data			X	X	X	X	X	X		
2	Evaluate C4 reach, effectiveness, and adoption								X	X	X
	Evaluate C4 implementation (time motion studies)			X	X	X	X	X			
3	Develop costing tools	X	X								
	Collect cost data			X	X	X	X	X			
	Cost-effectiveness analyses and development of costed implantation plan								X	X	X
	Publications, dissemination								X	X	X

10. Inclusion and Exclusion Criteria

Eligible PPFP providers will be women working in L&D or family planning at one of the study facilities. Eligible Happy Client promotors will be postpartum women who received promotions and selected a PPFP method. Eligible nurse/midwife and CHW promotors will be women working as nurses or CHWs at one of the intervention facilities. All women eligible for PPFP services in this study will be at any stage of pregnancy or up to 14 weeks postpartum, and receiving ANC, L&D, IV, or postpartum services at one of the intervention or pilot facilities.

We will NOT exclude:

- Pregnant women or Postpartum women of any age

We will exclude:

- Prisoners

Not applicable:

- Adults unable to consent (waivers of consent/assent/parental permission will be sought for all participants)

11. Vulnerable Populations

C4 counseling provided to pregnant women does not create additional risk for this population. C4 counseling is non-coercive and is delivered by trained nurses/counselors who will describe the benefits and possible side-effects of all PPFP method options. This

includes informing women as to the seriousness and likelihood of the side-effects and adverse events.

Methods of contraception will be offered to women and teenagers in accordance with US and Rwandan FDA regulations. No additional protections are required for method provision in teenagers.

12. Local Number of Participants

All women eligible for PPFP services in this study will be at any stage of pregnancy or up to 14 weeks postpartum, and receiving ANC, L&D, IV, or postpartum services at one of the intervention or pilot facilities. There will be no screening procedures. Based on facility volume and preliminary findings, we conservatively expect to deliver promotions in intervention facilities to 10,553 in the 10 intervention facilities (16% of reproductive age women in the catchment area). We expect to insert 3,060 PPIUDs and 1,161 PP implants in the 10 intervention facilities.

13. Recruitment Methods

Nurses, CHW, and Happy Clients will be recruited for training and refresher by convenience from the study facilities. PPFP providers will be recruited for training from all women with experience working in L&D or family planning at one of the study facilities in Kigali, Rwanda. No retention plan is necessary. Women receiving C4 services will not be recruited; all women receiving care at one of the selected facilities during the intervention time period will be offered C4. To increase follow-up, we will also provide CHWs with lists of clients in their catchment areas who are pending follow-up to remind those women about their appointments.

14. Withdrawal of Participants

PPFP counseling/service delivery recipients are free to withdraw at any point in the program, including discontinuing ANC care or delivering at different facilities.

15. Risks to Participants

Though contraceptive methods have extremely favorable safety profiles, all contraceptive have side-effects.

- Copper IUD. Non-serious side-effects include pelvic pain (12%), heavy menstrual bleeding (5%), ovarian cysts (4%), and dysmenorrhea (3%). These side-effects tend to be worse for the first 3-6 months after insertion and then improve. Serious side-effects include infection (5%), perforation of the uterine wall (occurring in 1.6% of women), pelvic inflammatory disease (PID) (occurring in 0.5% of women and typically during first 3 weeks after insertion), and menorrhagia (i.e., heavy bleeding requiring treatment, 0.2%).
- Hormonal methods (implant, oral contraception, injectables). Common non-serious side-effects include weight gain (46%), headaches (12%), irregular or painful periods (8%), acne (5%), and nausea (4%). Serious side-effects include blood clot (<1%). Insertion site infections may occur with implant insertion (0.8%).

- Tubal ligation. Non-serious side effects include minor bleeding (5%). Serious side-effects include severe bleeding (0.5%), severe pain (0.4%), and infection (1%).

16. Potential Benefits to Participants

Women participating the C4 services may benefit from improved education about, access to, and uptake of PPFP. The potential risks to subjects are reasonable in relation to these anticipated benefits.

17. Compensation to Participants

Women who receive a PPFP method will not be compensated, nor will they incur additional expenses for participating in the program. PPFP follow-up visits will be scheduled during regular clinic follow-up (e.g., infant vaccination visits) and management of side-effects will be covered by insurance (mutuelle), which covers >90% of women. Provision of care for uninsured women will be paid for by the study.

18. Data Management and Confidentiality

Based on facility volume and preliminary findings, we conservatively expect to deliver promotions in intervention facilities to 10,553 in the 10 intervention facilities (16% of reproductive age women in the catchment area). We expect to insert 3,060 PPIUDs and 1,161 PP implants in the 10 intervention facilities. Given facility volume and previous experience, service delivery to this number of women is highly feasible. Sample size and power calculations account for intra-cluster correlation (ICC) which considers between cluster correlation, within cluster correlation, and repeated measures. We assume pooled between and within cluster ICCs and a homogeneous intervention effect over time.

Table. Expected deliverables during study time period, n=10 intervention facilities. Power to detect differences between standard of care control and intervention: >80%.

	Control [a]			Intervention		
Stakeholders	**N events**	**Denominator**	**Expected %**	**N events**	**Denominator**	**Expected % [b]**
Clinic directors engaged	2	10	20%	10	10	100%
Promotions						
Nurses [b] trained to promote PPFP	6	178	3%	81	178	46%
CHWs trained to promote PPFP	0	260	0%	56	260	22%
Providers at implementation facilities						
Providers trained to insert/provide PPFP	6	134	4%	65	134	48%
Providers certified to provide PPFP	0	134	0%	58	134	43%
Clients delivering at implementation facilities						
Promotions to pregnant or postpartum women/couples	222	14,832	1%	10,553	14,832	71%
PPIUD insertions	17	222	7%	3060	10,553	29%
PP implant insertions	12	222	5%	1161	10,553	11%

[a] Data from n=10 government clinic logbooks, 2018.
[b] Estimated from the pilot study.
[c] In ANC, L&D, FP, and IV.

Reach and adoption. We will tabulate, overall and by facility, the number of stakeholders engaged, providers trained, promoters trained; providers certified and pre/post-training evaluation scores; and clients who received one-on-one counseling. We **hypothesize** increases comparing C4 versus standard of care in: stakeholders engaged, providers trained to promote and provide PPFP, couples/clients receiving information about PPFP (**Table 5**). We expect 90% of trainees will receive certification and provide PPFP.

Effectiveness.

Study objectives will be addressed using two statistical models, one based on data aggregated at the cluster-level, and another based on participant-level data. The effect of the intervention compared with the control on the uptake of a PP LARC method (IUD or implant, modeled separately) will be quantified using the cluster-level model. The association of the uptake of PP LARC with the type and timing of promotions will be examined using a participant-level model based on data collected during the intervention phase.

Model 1: Research question to be addressed: is there a difference in PP LARC uptake when comparing intervention vs. control?"

$$Y_{ij} = \beta_0 + \beta_1*(intervention_{ij}) + \beta_2*(covariate_{ij}) + \beta_3*(intervention_{ij} * covariate_{ij}) + u_i + e_{ij}$$

where
i = cluster (1,2,3,4)
j = time period (quarter 1,2, …,10)
Y_{ij} = the number of uptakes of a particular method in cluster i during time period j. Separate models will be implemented for implant and IUD uptake numbers.
$intervention_{ij}$ = 0 if cluster i is in the standard of care (control) phase in time period j, 1 if it is in the intervention phase
β_k = fixed effect for intervention (k=1), covariate (k=2), interaction (k=3)
u_i = random effect for cluster
ε_{ij} = random error

Several covariate and interaction terms will be examined, including time period, average facility volume, average service volume-to-staffing ratio, and total number of promotions received.

Model 2: Research question to be addressed: are the type of promotion and the timing of promotions associated with the uptake of a PP LARC method?

$$\begin{aligned} logit(Y_{ijl}) = {} & \beta_0 + \beta_1*(PS1_{ijl}) + \beta_2*(PS2_{ijl}) + \beta_3*(PS3_{ijl}) + \beta_4*(PS4_{ijl}) + \\ & \beta_5*(PT1_{ijl}) + \beta_6*(PT2_{ijl}) + \beta_7*(PT3_{ijl}) + \beta_8*(PT4_{ijl}) + \beta_9*(\#\ promotions) + \\ & \beta_{10}*(cluster\ covariate_{ijl}) + \beta_{11}*(participant\ covariate_{ij}) + u_i + v_l \end{aligned}$$

where
i = cluster (1,2,3,4),
j = time period (quarter 1,2, …,10)
l = participant (1,2, …, n_i)
Y_{ijl} indicates whether or not, in the ith cluster, in time period j, there was a method uptake for the lth participant. There are n_i participants in the ith cluster. Separate models will be implemented for implants and IUDs.

Promotion strategies or types experienced (yes or no) by the lth participant in the ith cluster, in time period j:
$PS1_{ijl}$ = video promotion
$PS2_{ijl}$ = happy client promotion
$PS3_{ijl}$ = community health worker promotion
$PS4_{ijl}$ = male partner present during promotion

Times/stages of promotions (yes or no) to lth participant in the ith cluster, in time period j:
$PT1_{ijl}$ = labor and delivery
$PT2_{ijl}$ = postpartum ward
$PT3_{ijl}$ = ante-natal
$PT4_{ijl}$ = infant vaccination

β_1 *through* β_8*:* fixed effects for promotion strategies/types and timings
β_9*: fixed effect for total number of promotions (at any time)*
β_{10} : fixed effect for a cluster-level covariate (multiple such terms to be included, as specified below)
β_{11} : fixed effect for an individual-level covariate (multiple such terms to be included, as specified below)
u_i = random effect for cluster
v_l = random effect for participant

Cluster-level covariates will be similar to those in Model 1. Participant-level covariates will include demographic characteristics.

Missing data. Given uncertainty associated with imputing data, primary analyses will be complete case analyses (i.e., missing data will not be replaced). Sensitivity analyses using multiple imputation will evaluate the impact of missing data on results using the fully conditional method in SAS.

Crossover effects. The potential for crossover is possible if nursing staff are redistributed during the study. The MOH will limit redistribution in study facilities during the intervention to only what is necessary (e.g., due to staff shortages) (*letter of support*). Additionally, it is possible that women could receive promotions in an intervention study facility and then deliver in a control study facility where they request PPFP. We will attempt to limit such events by encouraging women to consistently receive ANC, L&D, and IV services at the same clinic (generally beneficial

to women since medical records are not easily linked across facilities). Transfers between intervention and control facilities will be recorded to quantify the potential effect of crossover.

Cost C4 and standard of care. Following Global Heath Cost Consortium guidance [3], we will report PPFP financial costs of actual expenditures by using standard micro-costing methods [4, 5] to calculate the incremental cost of the intervention. We include both development costs (i.e., project start-up) and implementation costs (i.e., on-going costs to deliver the intervention, including management of side-effects). We exclude research costs (e.g., patient consenting, interviews, research data analysis). Primary data will be collected by carefully tracking costs during the implementation using accounting records, logbook data, and time motion studies. Costs to participants will include the time spent during PPFP provision, follow-up, and management of side-effects (converted into opportunity costs using household income). Cost of contraceptive methods will be estimated from the literature [6]. Costs will be categorized into activity type, and each demand creation strategy will be costed separately. Cost data will be entered into a standardized excel spreadsheet with embedded formulae to calculate costs by expenditure category and adjusted to US dollars of the year of data analysis. Straight-line depreciation for capital goods will be applied to give an annual cost over the life of the project [7]. We will present the total undiscounted costs to facilitate a MOH budget impact analysis. Time horizons of 1, 3, and 5 years are selected to be relevant for budget planning. The reduction in costs after social diffusion [8] is reached and the need for demand creation decreases (conservatively assumed to occur once 50% of the target population has been reached with C4 messaging) will be estimated to provide data to support sustained promotions until social diffusion is reached.

Estimate C4 cost-effectiveness versus standard of care. We adhere to Consolidated Health Economic Evaluation Reporting Standards [9]. The primary outcome of interest is cost per CYP gained for each PPFP method. CYP for contraceptive methods will be calculated adjusting to remove 'double coverage' caused by overlap with postpartum lactational amenorrhea. We will also evaluate the cost-effectiveness of each PPFP demand creation strategy (CHW, 'Happy Client's and video-based), providing new, critical information for decision-making. Parameters and costs will be derived from study data and the peer-reviewed literature. Including published estimates of: CYPs [10, 11]; costs to the healthcare system for contraception [6], costs associated with adverse pregnancy outcomes (preterm birth, maternal death, neonatal death) [12-16]; and healthcare visits, and management of side-effects [17]. Costs and CYP gained will be discounted at an annual rate of 3% [18-20]. We will report outcomes using time horizons assuming one year, three years, and five years of PPFP method use. TreeAge Pro 2019 will be used to calculate the incremental cost-effectiveness ratio (ICER) for C4 vs SOC as: ($Cost_{intervention}$ – $Cost_{StandardofCare}$) / ($Outcome_{intervention}$ – $Outcome_{StandardofCare}$)]. Bootstrapping will be used to calculate the confidence interval around the ICER [21]. Based on preliminary data [2, 22], we expect lower costs per CYP for PP LARC versus non-LARC methods, despite their heavier investment in provider training, reimbursements, and mentorship. This is due to the higher effectiveness and lower commodity cost per year for LARC methods versus non-LARC methods, as well as the time saved by providers and women due to decreased clinic visits required for LARC users (e.g., they do not have to return for monthly pill refills or 3-monthly injections).

Estimate C4 cost-utility versus standard of care. Units of effectiveness expressed in quality-adjusted life years (QALYs) is a generic measure of disease burden including both the quality and the quantity of life lived and is widely recognized as a useful approach for measuring and comparing different health interventions [23]. We will calculate cost-per-QALY saved over a lifetime horizon. Parameters and costs will be derived from study data and the peer-reviewed literature including published estimates of: costs to the healthcare system for contraception, adverse pregnancy outcomes (preterm birth, maternal death, neonatal death) [12-16]; and healthcare visits including for management of side-effects [17]. To translate the impact of preterm births, maternal deaths, and neonatal deaths averted into QALYs saved, we will apply a utility score (where 1 is perfect health and 0 is death) using the most up-to-date estimates from the literature (for example, the 2017 Global Burden of Disease Study [24]) and published life expectancy estimates for Rwanda for participants in our study given their age at enrollment. Costs and QALYs saved will be discounted at an annual rate of 3% [18-20]. The cost-per-QALY saved is calculated as $(Cost_{intervention} - Cost_{StandardofCare})/Q*\Delta X$ [25, 26] where ΔX denotes the total outcomes averted by the intervention vs standard of care and Q is the number of QALYs saved for each outcomes averted. Bootstrapping will be used to calculate the confidence interval around these ratios [21]. C4 will be considered "cost-saving" if it saves QALYs and costs less relative to standard of care. C4 will be considered "cost-effective" if the cost-utility ratio is less than 3 times the per capita gross domestic product. Affordability within existing national budgets will also be considered [27]. We hypothesize C4 will be cost-saving from a societal perspective compared to standard of care due to substantial savings accrued by averting preterm birth, maternal and neonatal deaths, and decreased burden on healthcare providers and clients.

Sensitivity, scenario, and threshold analyses. One-way sensitivity analyses of all parameters (varying each parameter by +/-20%**)** will determine which inputs the cost-effectiveness estimates are most sensitive to. We will also conduct Monte Carlo probabilistic sensitivity analyses in which multiple parameters with the most uncertainty are simultaneously varied following a selected distribution. Importantly, the cost model can be fit with parameters from scenarios representing to estimate the cost-effectiveness of C4 in different settings or scenarios (e.g., reduced costs of demand creation after social diffusion is reached, task shifting more PPFP provision to midwives). These scenario analyses will ensure that we parameterize our models in ways that are flexible for use in other settings. This will also allow us to explore parameter value thresholds at which recommendations would change.

Data management and quality assurance. PPFP logbooks will be maintained by trained PPFP providers in government facilities. Logbook data will be extracted into tablets weekly by the research field team through the mobile data collection platform Survey CTO v2.41 (Dobility, Cambridge, USA). Survey CTO data will be downloaded for weekly query and cleaning in a Microsoft Access database. Data will then be imported into SAS (Cary, NC) for analysis. A unique code will track clients from the community through ANC, L&D, and IV. This unique code is composed of personal information that the participant would remember (e.g., first three letters of mother's name) but is unlinked to identifiers. We used this code in our previous C4 pilot and

were able to track >95% of women who attended multiple visits at ANC, delivery/postpartum, and/or infant vaccination. For qualitative assessments, de-identified transcribed audio recordings will be stored on a secure server.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

As in our pilot study, implementation clinic facility staff will be trained to collect AEs and SAEs from patients for recording within pre-created government clinic logbooks (which detail the incident, actions taken, supervisor notes, and follow-up steps). Any unanticipated problems and (serious) adverse events following participation will be tracked via referral and clinician follow-up. Events will also be recorded on a study adverse event log. These data are later abstracted by our research staff for electronic data entry.

We will closely track incoming numbers of participants via ongoing recruitment activities, and weekly and monthly reports will be compiled by the study staff. We will utilize similar procedures to monitor any missing data or missed follow-up assessments. Unanticipated problem and (S)AE data reports will be monitored by the Study Coordinator, PI, and the study statistician (see *DSMP*). All data will be protected on firewall-protected servers at Emory and the Rwanda coordinating site. Any identification of recruitment rates or follow-up rates that represent threats to our ability to sufficiently answer the research questions will be met with action by the PI to intervene to remedy the shortcomings.

Interviewers and intervention staff will report any breach of confidentiality incurred by the participants to the Study Coordinator, who will then inform the PI. Any participant in need of treatment due to receiving contraception will be referred for appropriate services.

The study adverse event log, supplemented by any additional staff notes will be provided to the appropriate agencies, including the Rwandan and Emory IRBs and NIH. Any resulting recommendations from the IRB will be communicated to NIH. The PI will be responsible for daily monitoring and reporting of any adverse events and will involve the DSMB. The study statistician prepares reports that list adverse events, serious adverse events, deaths, and disease-or treatment-specific events required for monitoring body review in order to ensure good clinical care and identify any emerging trends. PI Wall will follow the Emory and Rwandan IRB and Office for Human Research Protections (OHRP) reporting requirements.

Any incidents involving subject safety will be reported to all institutional IRBs and the NIH per the DSMP (see DSMP).

Interim analysis of the study (S)AEs will be conducted at the midpoint of year 3. The difference between the proportion of events (the test statistic) in C4 versus the expected rate of (S)AEs associated with each contraceptive method (from the published literature) will be quantified with p-values constructed for alpha=0.05, two-sided. If the test statistic exceeds the boundary, then the study could be considered for early termination. In the event of any adverse or life-threatening events occurring at an unacceptable level, the PI will take appropriate action to halt

the study, release a participant from the study, or modify the study procedures to reduce or eliminate the identified risk. Should a situation arise of insufficient power due to poor recruitment or early detection of (S)AEs the investigators will discuss halting the study, when and if needed, and would report such action to the Emory and Rwandan IRB, the DSMB, and the NIH project officer. Completion rates of intervention activities will be monitored in parallel fashion.

The DSMB will act in an advisory capacity to the NIH to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. The DSMB will meet in-person/Zoom conference at the outset of the study, and thereafter by conference call twice per year scheduled around particular milestones of the study, e.g.,: prior to study initiation (for review of surveys, materials, protocols, etc.), approximately half way through recruitment (to ensure adequate recruitment, review progress, protocol fidelity, etc.), at the conclusion of intervention delivery, and a session for final results. Safety reports are sent to the DSMB twice a year and will include a detailed analysis of study progress, data and safety issues (see DSMP). Specific triggers for an ad hoc review or initiation of the process of an ad hoc review will occur if there are unforeseen deaths related to the study (see DSMP).

In addition we will convene a local Community Advisory Board (CAB) at the beginning of the study with meetings every 6 months to share the study design, study findings and learn more about the community perceptions, barriers and facilitators to postpartum contraception.

20. Provisions to Protect the Privacy Interests of Participants

No PHI will be collected under this protocol. Nurses/counselors trained to deliver C4 counseling and PPFP provision will be trained to deliver these services in a non-coercive way that is responsive to women's fertility and family planning method desires. Client age and parity will be abstracted from government Family Planning logbooks.

21. Economic Burden to Participants

Participants will incur no direct costs during the project.

22. Consent Process

We request a waiver of consent, assent, and parental permission.

Non-English-Speaking Participants

Participants speak Kinyarwanda. All oral and written information provided to participants will be in Kinyarwanda

Participants who are not yet adults (infants, children, teenagers)

There is no legal age for consent to treatments or procedures involved in the study. No PHI will be collected in this study. We request a waiver of assent and parental permission.

Cognitively Impaired Adults

Not applicable

Adults Unable to Consent

Not applicable

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

We request a waiver of informed consent, assent, and parental permission.

23. Setting

The Rwanda Zambia HIV Research Group (RZHRG) has been a global leader HIV prevention and family planning research. RZHRG is committed to the research and promotion of long-acting user-independent methods of contraception. Projet San Francisco (PSF)/CFHR was established in Kigali, Rwanda in 1986 by Dr. Susan Allen. **Projet San Francisco (PSF)/Center for Family Health Research (CFHR)** is an accredited non-profit organization based in Kigali, Rwanda committed to the pursuit of excellence in research and service delivery to improve family planning and prevent HIV and related infections. **PSF/CHFR will oversee all in-country implementation activities.**

PSF/CFHR is located in the nation's capital, Kigali. PSF/CFHR is comprised of buildings which house a filing unit, medical enrollment, medical clinic, pharmacy, phlebotomy, Good Clinical Laboratory Practice (GCLP) accredited laboratory (serology, microscopy, ELISAs, hematology, immunology, clinical chemistry, flow cytometry and PCR), administration, data unit and archive. Both the laboratory and pharmacy are equipped to conduct HIV vaccine clinical trials and continue on this endeavor through support from the International AIDS Vaccine Initiative (IAVI). All departments are equipped with appropriate materials to carry out the scope of work including a server and back-up server, over 20 computers, 5 printers, 2 photocopiers, onsite IT support, air-conditioners. The site has 4 vehicles for logistics, a backup generator for power outages and 24-hour security. The PSF/CFHR laboratory is externally audited three times a year for technical competence and GCLP adherence and internally monitored by study sponsor (IAVI) twice annually. Additionally, the laboratory is enrolled in external quality assurance (EQA) programs for all diagnostic testing done onsite (HIV/RPR serology, urine & clinical chemistry, hematology, pregnancy, and flow cytometry). The site is internally monitored by IAVI; quarterly for medical and data and twice annually for administration/finance compliance.

PSF/CFHR is directed by Etienne Karita MD MSPH MSc who is supported by a team of study physicians, senior research nurses, counselors, laboratory scientists, data technicians, administrative assistants, filers, general workers, interns (MPH or MD/MPH) and project

coordinators. All medical, data and lab staff are Human Subjects trained and Good Clinical Practice (GCP) certified. In addition, lab staff are GCLP certified. The site uses RZHRG standard operation procedures (SOPs) to conduct all scopes of work. SOP training and competency assessments occur annually with bi-annual SOP review. The PSF/CFHR site benefits from long standing relationships with local NGOs as well as government organizations. Existing support from both CDC and IAVI leverage the costs of infrastructure as well provide physical, financial and intellectual resources. Furthermore, the RZHRG Emory team provides additional technical assistance to the site including scientific support, M&E, data management and supply procurement.

PSF/CFHR will implement C4 in 10 intervention facilities with high-volume L&D departments and will use our 5 pilot facilities as training sites. These 15 facilities include 13 health centers (which provide ANC, family planning, and IV, and refer L&D cases to adjoining hospitals) and 2 stand-alone hospitals (which provide routine L&D services and also receive referrals of high-risk and complex obstetric cases from health centers). All facilities have infrastructure for PPFP provision and procurement, though no formal PPFP initiatives are currently taking place, PP implant insertions are infrequent, and no providers are trained to insert PPIUDs. Our team has worked in these clinics (conducting clinic logbook data abstraction, implementing couples' HIV counseling and testing, implementing LARC services, and surveying providers and patients) for over 10 years.

We will convene a local Community Advisory Board (CAB) at the beginning of the study with meetings every 6 months to share the study design, study findings and learn more about the community perceptions, barriers and facilitators to postpartum contraception. All study procedures will be reviewed by the Rwandan Ethics Committee.

24. Resources Available

Facilities are high-volume government run health facilities in the capital of Kigali. All participants will have access to standard of care medical resources offered at these facilities. Serious side-effects will result in a referral for specialist care per current standard of care. All clinical care including management of side-effects will be provided by government facility personnel at health centers as part of usual care at no cost to the patient or health facility. Nurses/counselors will receive training and clinical and counseling support from already certified PPFP providers.

25. Multi-Site Research when Emory is the Lead Site

Not applicable

26. References

1. USAID and MCHIP. *Guide du Formateur: Fournir les Services de DIU du Postpartum*. 2013 [cited 2018 August 3]; Available from: https://www.k4health.org/sites/default/files/guide_formateur_revjuly2013.pdf.

2. Ingabire, R., et al., *Evaluation of a multi-level intervention to improve post-partum intrauterine device services in Rwanda.* Gates Open Research, 2018. **2**(38).
3. Global Health Cost Consortium. *Analyzing and presenting results: Principles 15-17*. 2020 [cited 2020 February 11]; Available from: https://ghcosting.org/pages/standards/principles/analysing_and_presenting_results.
4. Sanders, G.D., et al., *Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine.* Jama, 2016. **316**(10): p. 1093-103.
5. *Cost-effectiveness in Health and Medicine*. 2 ed, ed. S.G. Neumann PJ, Russell LB, Siegel SE, Ganiats TG. 2016, New York, NY: Oxford University Press.
6. Management Sciences for Health. *International Medical Products Price Guide* 2016 [cited 2020 June 15]; Available from: https://mshpriceguide.org/en/home/.
7. Walker, D. and L. Kumaranayake, *Allowing for differential timing in cost analyses: discounting and annualization.* Health Policy Plan, 2002. **17**(1): p. 112-8.
8. Rogers, E.M., *Diffusion of Innovations*. 3 ed. 1962, New York: The Free Press.
9. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.* Int J Technol Assess Health Care, 2013. **29**(2): p. 117-22.
10. Stover, J., J.T. Bertrand, and J.D. Shelton, *Empirically based conversion factors for calculating couple-years of protection.* Eval Rev, 2000. **24**(1): p. 3-46.
11. USAID. *Couple Years of Protection (CYP)*. 2014 [cited 2018 June 15]; Available from: https://www.usaid.gov/what-we-do/global-health/family-planning/couple-years-protection-cyp.
12. Sedgh, G., S. Singh, and R. Hussain, *Intended and Unintended Pregnancies Worldwide in 2012 and Recent Trends.* Studies in family planning, 2014. **45**(3): p. 301-314.
13. Institute for Health Metrics and Evaluation. *Health Service Provision in Zambia: Assessing Facility Capacity, Costs of Care, and Patient Perspectives*. 2014 [cited 2018 June 19]; Available from: http://www.healthdata.org/sites/default/files/files/policy_report/2014/ABCE/Zambia/ABCE_Zambia_full_report.pdf.
14. Koontz, S.L., et al., *Treating incomplete abortion in El Salvador: cost savings with manual vacuum aspiration.* Contraception, 2003. **68**(5): p. 345-51.
15. Rydzak, C.E. and S.J. Goldie, *Cost-effectiveness of rapid point-of-care prenatal syphilis screening in sub-Saharan Africa.* Sex Transm Dis, 2008. **35**(9): p. 775-84.
16. Parmar, D., et al., *Cost of abortions in Zambia: A comparison of safe abortion and post abortion care.* Global Public Health, 2017. **12**(2): p. 236-249.
17. Hitimana, R., et al., *Cost of antenatal care for the health sector and for households in Rwanda.* BMC Health Services Research, 2018. **18**: p. 262.
18. Jain, K.M., et al., *Cost and cost threshold analyses for 12 innovative US HIV linkage and retention in care programs.* AIDS Care, 2016. **28**(9): p. 1199-204.
19. Paltiel, A.D., et al., *HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness.* Clin Infect Dis, 2009. **48**(6): p. 806-15.

20. Juusola, J.L., et al., *The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men.* Ann Intern Med, 2012. **156**(8): p. 541-50.
21. Drummond, M.F., et al., *Methods for the Economic Evaluation of Health Care Programmes*. 2005, Oxford, England: Oxford University Press.
22. Wall, K.M., et al., *Rwandan stakeholder perspectives of integrated family planning and HIV services.* Int J Health Plann Manage, 2018. **doi: 10.1002/hpm.2586. [Epub ahead of print]. PMC6289844.**
23. Owens, D.K., *Interpretation of cost-effectiveness analyses.* Journal of general internal medicine, 1998. **13**(10): p. 716-717.
24. Institute for Health Metrics and Evaluation (IHME). *Findings from the Global Burden of Disease Study 2017*. 2018 [cited 2020 Jun 27]; Available from: http://www.healthdata.org/sites/default/files/files/policy_report/2019/GBD_2017_Booklet.pdf.
25. Pinkerton, S.D. and D.R. Holtgrave, *A method for evaluating the economic efficiency of HIV behavioral risk reduction interventions.* AIDS Behav, 1998. **2**: p. 189-201.
26. Pinkerton, S.D. and D.R. Holtgrave, *Assessing the cost-effectiveness of HIV prevention interventions: A primer*, in *Handbook of Economic Evaluation of HIV Prevention Programs*, D.R. Holtgrave, Editor. 1998, Plenum Press: New York. p. 33-43.
27. Marseille, E., et al., *Thresholds for the cost-effectiveness of interventions: alternative approaches.* Bulletin of the World Health Organization, 2015. **93**(2): p. 118-124.