STATISTICAL ANALYSIS PLAN

Co-produced Community Action for improved access to Cervical Cancer Screening (Act4CC)

Document information

Trial acronym	Act4CC
Principal investigator	Prof. Patrick Petignat, Geneva University Hospitals
Trial design	Two-arm, parallel-group, open-label cluster-randomized controlled trial (cluster-RCT), embedded within a mixed-methods participatory research project
Number of clusters	14 rural health areas (7 intervention, 7 control)
Target population	Women aged 30–49 years (25–49 years if HIV-positive) residing in a rural health area of the Mifi Health District, West Region of Cameroon
Primary outcome	Proportion of eligible women completing cervical cancer screening
SAP version	1.0 (validated 4 July 2026)
SAP status	Pre-analysis
Reference protocol	Act4CC protocol
Reporting guidelines	CONSORT 2010 extension to cluster-randomized trials; ICH E9 (R1); Gamble et al., JAMA 2017

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Abbreviations

aOR	Adjusted odds ratio
CC	Cervical cancer
CCA	Community co-produced action
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CONSORT	Consolidated Standards of Reporting Trials
DE	Design effect
GEE	Generalized estimating equations
GLMM	Generalized linear mixed model
HPV	Human papillomavirus
ICC	Intraclass correlation coefficient
ICH	International Council for Harmonization
IQR	Interquartile range
ITT	Intention to treat
RCT	Randomized controlled trial
SAP	Statistical analysis plan
SD	Standard deviation

1. Introduction and background

Cervical cancer is the fourth most common cancer in women worldwide, causing over 300,000 deaths yearly, and the leading cause of cancer death in women in Sub-Saharan Africa. The disproportionate burden in low- and middle-income countries reflects insufficient uptake of vaccination against human papillomavirus (HPV) and of screening for HPV infection and precancerous lesions. In Cameroon, only an estimated 4% of women of reproductive age have ever been screened. In 2020 the World Health Organization (WHO) launched a global initiative to eliminate cervical cancer as a public health problem, with targets of 90% HPV vaccination of girls, 70% screening of women with a high-performance test, and 90% treatment of women with precancerous lesions by 2030.

The Act4CC study evaluates whether community co-produced action (CCA), a community-based participatory action research approach to designing and implementing locally tailored screening strategies, can increase cervical cancer screening uptake in rural Cameroon when compared with a traditional hospital-based recruitment strategy.

The trial is embedded within a broader mixed-methods participatory research project; this Statistical Analysis Plan (SAP) covers the quantitative cluster-RCT component only.

1.1. Purpose of this SAP

This SAP pre-specifies the analyses for the Act4CC cluster-RCT. It is intended to:

- Minimize bias in the analysis by pre-specifying methods.
- Document analytical choices in sufficient detail to allow independent replication.
- Address known methodological challenges of the trial design — in particular the small number of clusters (k = 14) and the use of an aggregate denominator for the primary outcome.

This SAP follows the guidelines for the content of statistical analysis plans in clinical trials (Gamble et al., JAMA 2017), the principles of ICH E9 (R1) on statistical principles for clinical trials, and the CONSORT 2010 extension to cluster-randomized trials for the planned reporting of results.

1.2. Research question and hypothesis

Primary research question: does community co-produced action (CCA) increase the proportion of eligible women completing cervical cancer screening in rural health areas of the Mifi Health District, compared to a hospital-based screening standard procedure (as defined in the protocol)?

Null hypothesis (H_0): there is no difference between CCA-based screening and hospital-based screening in the proportion of women (aged 30-49 years residing in a rural area) completing cervical cancer screening within 18 months.

Alternative hypothesis (H_1): there is a difference between CCA-based screening and hospital-based screening in the proportion of women (aged 30-49 years residing in a rural area) completing cervical cancer screening within 18 months.

2. Objectives and estimands

2.1. Primary objective

- To estimate the effect of CCA on the proportion of women completing cervical cancer screening, compared with a traditional hospital-based recruitment strategy.

2.2. Secondary objectives

2.2.1. Evaluating the effect of CCA

- To estimate the effect of CCA on completion of primary HPV screening within 12 months.
- To estimate the effect of CCA on completion of triage within six months of HPV self-sampling, among HPV-positive women.
- To estimate the effect of CCA on immediate treatment, among triage-positive women.
- To estimate the effect of CCA on attendance of the 12-month follow-up visit among HPV-positive participants.

2.2.2. Descriptive

- To describe baseline characteristics of randomized health areas by study arm.
- To describe sociodemographic, behavioral and clinical characteristics of screened participants by arm.
- To describe HPV test results by arm, among screened participants.
- To describe triage results by arm, among triaged participants.
- To describe the distribution of HPV genotypes among HPV-positive participants, by study arm.
- To describe the distribution of cytology and histology results, and the presence of a high-grade lesion, among triaged participants, by study arm.
- To describe screening outcomes and number of eligible women screened prior to trial start by paired health area level, by arm.

2.2.3. Methodological

- To report the empirical design parameters of the trial to inform prospective sample-size calculations for future trials and to estimate the intraclass correlation coefficient (ICC) for the primary outcome.

2.3. Estimand framework

Following the estimand framework introduced in the ICH-E9 addendum (ICH 2020), the attributes of the estimand built around the primary endpoint are defined as follows:

Population	Women aged 30–49 years residing in one of the 14 rural health areas of the Mifi Health District at the date of cluster activation (t_0), who have no documented history of cervical cancer screening in the 5 years preceding (or 3 years if HIV positive), as enumerated through the population registry. HIV-positive women aged 25–29 years are eligible for the intervention but are excluded from the main analyses (see §6.3).
Intervention	Cluster-level allocation to the community co-produced action (CCA) arm versus the standard hospital-based recruitment arm. Comparison: CCA versus hospital-based.
Endpoint	Binary indicator of complete cervical cancer screening, defined at the individual level as either: (i) HPV-negative result on HPV self-sampling completed within the cluster's 12-month self-sampling window, or (ii) HPV-positive result on HPV self-sampling completed within the cluster's 12-month self-sampling window, followed by triage completed within 6 months of HPV self-sampling.
Population-level summary	Adjusted risk ratios (RR) with a 95% confidence interval.
Intercurrent events and handling strategy	All clusters are analyzed in the arm to which they were randomized (intention-to-treat at the cluster level), regardless of implementation fidelity. Individual-level intercurrent events such as pregnancy arising during follow-up or exposure of control-arm women to CCA-related communication are addressed via a treatment policy strategy: eligible women are counted in the denominator of their randomized cluster regardless of these events.

3. Trial design

3.1. Design summary

Act4CC is a two-arm, parallel-group, open-label, cluster-randomized controlled trial embedded within a mixed-methods participatory research project. The unit of randomization is the rural health area (cluster). The 14 rural health areas of the Mifi Health District are randomized 1:1 to the CCA arm or the standard hospital-based recruitment arm (7 clusters per arm). Randomization takes place within pairs of health areas matched on the estimated number of eligible women and distance to the reference screening center. Outcomes are ascertained according to the cluster screening windows and individual triage windows defined in §4.1.

3.2. Study period and location

The study took place over two years between April 2024 and December 2026.

The study location is the rural health areas of Mifi district, in the West Region of Cameroon. Mifi district is divided into 20 health areas, among which 6 are urban (with a population of approximately 328,000) and 14 are rural (population of approximately 152,000). The 14 rural health areas included, as detailed in the study protocol, comprise an estimated population of approximately 152,000 individuals.

In September 2023, a new cervical cancer screening center opened in the Bafoussam Regional Hospital as part of the GENOVA study, offering free screening and treatment of precancerous lesions to women of the Mifi Health District and neighboring areas.

3.3. Trial interventions

3.3.1. Intervention

The intervention is community co-produced action (CCA), a community-based participatory approach in which one or more locally tailored strategies to increase uptake of HPV-based cervical cancer screening are co-developed with community members and other stakeholders, and then implemented over a 12-month period. The CCA process in each intervention health area is coordinated jointly by local researchers and the chief health care provider of the health area (the health area leader), and consists of participatory workshops followed by the rollout of the co-developed strategies. The range of strategies that may emerge from the co-production process is broad and includes (but is not limited to) engagement of community health workers and local associations, health-area-level awareness campaigns, development of culturally appropriate educational materials, integration of primary HPV screening at local integrated health centers, and organization of group transportation to the district screening center. Because the specific strategies are co-defined with each community, the exact content of the intervention varies across intervention clusters by design.

3.3.2. Control

Health areas in the control arm receive the standard hospital-based recruitment strategy used in the Mifi Health District, coordinated centrally from the Bafoussam Regional Hospital. This consists of the training of two community health workers per health area, who conduct door-to-door visits and community meetings to raise awareness of cervical cancer and distribute nominal invitation vouchers to eligible women, with periodic feedback sessions over the trial period. Full operational details are reported in the trial protocol.

3.4. Randomization and blinding

Randomization is performed within matched pairs of health areas, in order to ensure balance across the study conditions on potential confounders due to the limited number of groups to be randomized. Prior to randomization, the 14 rural health areas are coupled into 7 pairs based on two matching variables: the estimated number of eligible women aged 30–49 years in the health area, and the distance to the reference screening center. Within each pair, one health area is randomly allocated to the CCA arm and

the other to the standard hospital-based recruitment arm, using a manual random draw (1:1). The intervention cannot be blinded to participants or implementers.

3.5. Interim analysis and stopping guidance

No interim analysis is planned. The intervention is non-invasive and non-clinical, and presents minimal risk of harm to participants; no stopping rules are therefore specified.

3.6. Timing of final analysis

The analysis will be performed after the SAP has been signed off.

4. Outcomes

4.1. Definition of follow-up windows and timing of outcome assessment

All trial outcomes are ascertained at the individual level from data recorded during the screening pathway (HPV self-sampling, triage, and treatment visits). Ascertainment is defined by two pre-specified windows operating at two different levels:

- **Cluster-level HPV screening window:** Each of the 14 health areas has a pre-specified 12-month calendar window during which HPV self-sampling is operationally available in that cluster. Cluster windows are fixed by the trial protocol prior to randomization and may overlap across clusters (some clusters share the same calendar window) or be distinct, depending on operational planning. A self-sampling event counts toward HPV primary screening completion only if it occurs within the cluster's window.
- **Individual-level triage window:** For each HPV-positive woman, the triage window is the 6 months following her individual self-sampling date (not the end date of her cluster's screening window). A triage event counts toward the relevant outcomes only if it occurs within these 6 months.

The maximum elapsed calendar time between the opening of a cluster's screening window and the ascertainment of all primary outcome status determinations for that cluster is therefore 18 months (12-month cluster self-sampling window + up to 6 months of individual triage follow-up for a woman self-sampling on the last day of the cluster's window). Outcome status is determined at the end of this 18-month period.

4.2. Primary outcome

The primary outcome is complete cervical cancer screening. Complete screening is defined at the individual level as either:

- HPV self-sampling within the cluster's 12-month screening window with an HPV-negative result, or

- HPV self-sampling within the cluster's 12-month screening window with an HPV-positive result followed by triage within 6 months of the woman's self-sampling date.

Women who returned an HPV self-sample that yielded an invalid test result and did not complete a repeat self-sample are classified as no complete screening (denominator).

Operationalization in the analysis dataset:

Numerator	Number of women aged 30–49 years in the health area who completed screening as defined above, derived from individual-level study records.
Denominator	Estimated number of eligible women aged 30–49 years per health area, defined as the census-based count (registry data) for the relevant age range minus women already screened in the 5 years (or 3 years if HIV positive) before the study within the eligible window.
Indicator estimation	Adjusted RR with its 95%CI.
Non-screened women	Derived by subtraction at the health area level; no individual-level data will be available for this group.
Timing	Ascertained over each cluster's pre-specified 12-month HPV screening window plus up to 6 months of individual triage follow-up, as defined in §4.1.

4.3. Secondary outcomes

The secondary outcomes are listed below:

- HPV primary screening completion (binary): completion of HPV self-sampling within the cluster's 12-month screening window, among eligible women, by arm.
- Triage completion (binary): completion of triage within 6 months of HPV self-sampling, among HPV-positive participants, by arm.
- Immediate treatment (binary): receipt of immediate treatment, among triage-positive women. Reasons for non-immediate treatment will be summarized according to main categories: large lesions ineligible for thermal ablation, suspicion of cervical cancer, technical issues and participant refusal, by arm.
- Attendance of the follow-up visit categorized as yes or no, by arm (binary). Attendance is assessed over a window opening at the woman's individual primary HPV screening (self-sampling) date and extending to 12 months + 1 month afterwards. The one-month margin accommodates reminder visits. A visit occurring within this window is counted as attended; a visit beyond 13 months, or no visit, is counted as not attended.

5. Cervical cancer screening process variables

- HPV test result: distribution of HPV test results, categorized as positive, negative, or non-valid, among women who completed primary HPV screening, by arm.
- HPV genotype distribution among HPV-positive participants, by arm, categorized as:
    - Group 1a: HPV 16
    - Group 1b: HPV 18/45
    - Group 1c: HPV 31/33/35/52/58
    - Group 1d+: HPV 51/59/39/56/66/68
    - Multiple channels
- Triage result: distribution of triage results, categorized as positive, negative, or missing, among women who completed triage, by arm.
- Cytology results distribution among triaged participants, by arm, categorized as:
    - No dysplasia
    - Atypical Squamous Cells of Undetermined Significance (ASC-US)
    - Low-grade Squamous Intraepithelial Lesion (LSIL)
    - High-grade Squamous Intraepithelial Lesion (HSIL)
    - Atypical Squamous Cells, cannot exclude HSIL (ASC-H)
    - Atypical Glandular Cells (AGC)
    - Cancer
    - Not valid
    - Missing
- Histology results distribution among triaged participants, by arm, categorized as:
    - No dysplasia
    - Cervical Intraepithelial Neoplasia grade 1 (CIN1)
    - Cervical Intraepithelial Neoplasia grade 2 (CIN2)
    - Cervical Intraepithelial Neoplasia grade 3 (CIN3)
    - Cancer
    - Not valid
    - Missing
- Presence of a high-grade lesion (binary) among triaged participants, by arm, defined as CIN2 or higher (CIN2+) on histology, or HSIL/cancer on cytology.

6. Other variables

The following variables provide contextual information to support interpretation of the trial results and to inform the design of future cluster-randomized trials in similar settings.

6.1. Cluster-level

- Baseline health area characteristics by arm: number of women, number of villages, number of health facilities, distance to center and transportation cost.
- Empirical design parameters: cluster size (individually and by health area pair).
- Intraclass correlation coefficient (ICC) with 95% confidence interval of the primary outcome.

6.2. Participant-level

Characteristics of women who completed HPV screening:

- Age (years)
- Source of information, categorized as:
    - Community health worker
    - Word of mouth
    - Radio or poster
    - Health care worker
    - Other
- Relationship status, categorized as:
    - Single
    - In relationship
    - Married
    - Widow/Divorced
- Educational level, categorized as:
    - No formal
    - Primary
    - Secondary
    - Tertiary
    - Other
    - Missing
- Occupation, categorized as:
    - Housewife
    - Agricultural worker
    - Salaried without responsibilities
    - Salaried with responsibilities
    - Freelance
    - Other
- HIV status: positive, negative or unknown
- Contraception use: yes or no
- Tobacco use: yes or no

- Parity
- Number of lifetime sexual partners
- Age at first sexual intercourse
- Sexual intercourse in past 12 months: yes or no
- Previously screened for cervical cancer (any time): yes or no

7. Sample size and power

7.1. A priori calculation (as defined in the protocol)

The a priori calculation assumed an absolute difference of 3.5 percentage points (from 3.5% in the control arm and 7.0% in the intervention arm), two-sided $\alpha = 0.05$, and 80% power, requiring 632 women per arm in an individually randomized design (1,264 total; OpenEpi v3). Randomization at the level of 14 health areas, with an assumed intraclass correlation coefficient (ICC) of 0.01 and a cluster size ($\bar{m}$) of approximately 1,086 eligible women, yields a design effect (DE) of:

$$\mathbf{DE = 1 + ICC \times (\bar{m} - 1) \approx 11.85}$$

giving a required total of approximately 14,978 women across both arms. Against an estimated eligible district population of ~15,200 women, the protocol concluded that the trial was designed to be on the borderline of adequate power if all assumptions held.

7.2. Methodological considerations of the a priori sample size calculation

The protocol's design effect formula assumes equal cluster sizes. In practice, the 14 health areas vary in population size. Eldridge et al. (2006)[1] show that the equal-cluster-size formula underestimates the true design effect when cluster sizes are heterogeneous; the appropriate formula becomes:

$$\mathbf{DE = 1 + (cv^2 + 1) \times (\bar{m} - 1) \times ICC}$$

where cv is the coefficient of variation of cluster size computed empirically from the 14 individual health-area eligible populations (Method 4 of Eldridge et al[1]). The resulting SD is 478, mean is 663 and cv is 0.72, yielding a corrected DE of 11.1 and a corrected sample size requirement of 13,986 women.

8. Statistical principles

8.1. Confidence intervals and p-value

All estimates of differences between the intervention and control group will be reported with 95% confidence intervals and p-values associated with a two-sided test at the 5% significance level.

8.2. Adjustment for multiplicity

There will be no correction for multiplicity testing (single primary outcome). All secondary analyses will be considered as exploratory and hypothesis-generating.

8.3. Analysis populations

All analyses will follow the intention-to-treat (ITT) principle at the cluster level: all 14 randomized health areas will be analyzed in the arm to which they were allocated, irrespective of the extent or fidelity of intervention implementation. No per-protocol analysis is planned due to the design of the study.

For consistency across outcomes, all analyses will be restricted to women aged 30–49 years. This restriction reflects the limits of registry-based denominators: reliable population counts are available only for this age range. Applying the same age window across all outcomes ensures that comparisons between arms and between cascade stages are based on a homogeneous population, free from composition effects driven by differential inclusion of HIV-positive women aged 25-29.

The operational definitions of denominators, numerators, and analysis populations applying this 30–49 restriction are detailed below, separately for the primary outcome and HPV test coverage (which share a registry-based denominator) and for cascade secondary outcomes (which use within-cascade denominators).

8.3.1. Analysis population for the primary outcome and HPV screening

All women aged 30-49 years residing in the health area of each cluster at t_0, as enumerated in the registry census. Women with a prior screening (in the last 5 years or 3 years if HIV-positive), identified through linkage with the GENOVA database, are excluded from the denominator at the registry level. Eligible women are counted regardless of any post-randomization event, including non-participation, refusal, ineligibility arising during follow-up, or exposure to non-randomized recruitment activities.

8.3.2. Analysis population for cascade secondary outcomes

Computed on individual-level data among women aged 30-49 who have entered the relevant stage of the screening cascade. The analysis population specific to each secondary cascade outcome is defined in the corresponding outcome-specific section as the subset of screened women aged 30-49 having reached the relevant cascade stage.

8.4. SAP amendments and protocol deviations

Any deviations from this SAP will be documented with date, rationale, and approving author(s) in an appendix to the trial report. Substantial amendments to this SAP (changes affecting the primary analysis, the analysis populations, or the handling of missing data) must be agreed by the trial statistician and the principal investigator.

9. Trial population

9.1. Source and target population

The target population for the cluster-RCT is women aged 30–49 years (25–49 years if HIV-positive) eligible for cervical cancer screening who reside in a rural health area.

9.2. Eligibility criteria

9.2.1. Inclusion criteria

- Women aged 30–49 years (25–49 years if HIV-positive).
- Residence in one of the 14 rural health areas of the Mifi Health District.
- Ability to provide written informed consent.

9.2.2. Exclusion criteria

- Known cervical cancer.
- Symptoms compatible with cervical cancer.
- Previous hysterectomy.
- Terminal disease other than cervical cancer.
- Cervical cancer screening test within the last 5 years (3 years if HIV-positive).
- Pregnancy at the time of screening.
- Lack of capacity for discernment.

9.3. Recruitment and flow diagram

A flow diagram will describe the flow of clusters and participants throughout the trial. The diagram will include, in each arm, the estimated eligible population, the number of women excluded (and reasons), the number of women included in the analyses.

9.4. Withdrawals, loss to follow-up, ineligibility, and protocol deviations

Because the primary outcome denominator is the registry-based eligible population at the cluster level rather than individually recruited participants, individual loss to follow-up does not reduce the denominator. Inclusion in the denominator is determined by registry-based eligibility (women aged 30–49 in the cluster, excluding those already screened within the preceding 3-5 years) and not by individual enrollment or consent; consequently, no eligible woman can opt out of the denominator. Women who refuse participation or do not attend screening are counted in the denominator and contribute as non-events to the numerator. This reflects the population-level estimand of the trial, which targets complete cervical cancer screening across the entire eligible population of each cluster rather than only among women who engage with the recruitment strategy.

Women who become ineligible during their cluster's screening window — for example through death, move-out, pregnancy, hysterectomy, or diagnosis of cervical cancer outside the trial — are kept in the denominator and counted as non-events if they had not yet completed screening. This is consistent with the public-health interpretation of population coverage and with the treatment-policy strategy.

10. Analysis methods

10.1. General analysis approach for the evaluation of primary and secondary outcomes (intervention effect)

This section describes the analysis approach common to the primary and tested secondary outcomes. Outcome-specific definitions of numerator, denominator and unit of analysis are specified in the corresponding sub-sections.

The 12-month follow-up visit attendance outcome is pre-specified in this version of the SAP but will be analyzed secondly, when the corresponding data will be available in the trial database. Follow-up data will become available approximately one year after enrolment of the last participant (expected end of November 2026, with a one-month margin for reminders, i.e. end of December 2026). This outcome will be analyzed once the data are available following the approach.

10.1.1. Model

Each tested outcome (section 4.2 and 4.3) will be analyzed using a generalized linear mixed model (GLMM) with a binomial likelihood and logit link (NIH Research Methods Resources, 2026; Murray et al., 2020[2]). The model will include study arm (CCA vs hospital-based) and age stratum (30–34, 35–39, 40–44, 45–49 years) as fixed effects, and a random intercept for cluster (health area) and the HA pair (stratification variable). Age strata are defined based on age at t_0, computed from date of birth and the cluster's t_0 date. No further covariates will be adjusted for, in line with recommendations against adjustment on matching variables in cluster-randomized trials with a small number of clusters[3,4]. Models will be fitted using the *glmer* function (*lme4* packages, R). The estimation of the adjusted risk ratio will be obtained through a g-computation, while the standard error is computed via the delta method. Both will be handled by the *avg_comparisons* function (*marginaleffects* package, R).

10.1.2. Effect measures

The risk ratio (RR) comparing the CCA arm to the hospital-based arm will be reported as the primary effect measure, with a 95% confidence interval and a p-value. Results will be reported in a table like Table 4. As secondary analysis, the risk difference with its 95%CI will be reported. The predicted risk in both arms will be reported with their 95%CI.

10.2. Dataset construction

The analytical dataset for the primary outcome will be constructed at the individual level by combining three sources, reflecting the structure of data availability across the eligible population.

Women who never initiated screening have no individual record in the screening database. For these women, one row per non-initiating woman will be added to the dataset, with cluster identifier, age stratum derived from the registry-based age distribution (5-year categories: 30–34, 35–39, 40–44, 45–49 years), and outcomes coded as 0. The number of non-initiating women per cluster per age stratum will be derived by subtracting the number of initiating women in that stratum from the corresponding registry count. Women who initiated screening and obtained a valid HPV test result are represented by their individual records. Women who initiated screening but obtained an invalid HPV test result and did not return for repeat sampling are represented by their individual records, with age stratum derived from their individual data and outcomes coded as 0 except for HPV primary screening.

Prior to dataset construction, a data quality check will be performed at the cluster × age stratum level. If the number of women recorded in the screening database exceeds the corresponding registry count for any cluster × age stratum combination, this discrepancy will be flagged, investigated, and fixed before analysis proceeds. Possible causes include out-of-area recruitment, duplicate records, or registry under-enumeration. The resolution strategy will be documented and reported.

10.3. Descriptive analyses

Continuous variables will be summarized as mean, standard deviation, median, quartiles 1 and 3, and minimum and maximum; categorical variables will be summarized as counts and percentages. No hypothesis tests will be performed, in line with recommendations for cluster-randomized trials. Imbalance, if any, will be described and discussed qualitatively.

10.3.1. Cluster-level characteristics

Characteristics (section 6.1) of the 14 randomized health areas will be summarized by study arm to describe balance between arms after randomization. Results will be reported in a table like Table 1.

Screening outcomes (section 4.2 and 4.3) at HA pairs level will be summarized by arm, and results will be reported in a table like Supplementary Table S1. Pre-trial screening coverage will also be reported by HA pairs, defined as the number of women previously screened (based on study data from a previous trial in the same district) divided by the estimated eligible population from census data, and expressed as a percentage. Results will be reported in a table like Supplementary Table S2.

10.3.2. Participant-level characteristics

The characteristics of the screened participants will be described separately for each study arm, and results will be reported in two tables. A table like Table 2 will present the sociodemographic characteristics of women who achieved complete screening (the primary outcome). A supplementary table will describe, using the same structure, the characteristics of women with a unique invalid HPV test result and women with an HPV-positive result who did not complete triage, by study arm.

These descriptive results will characterize the equity profile of each recruitment strategy (which women each strategy reaches) and will be discussed qualitatively in the final report.
Primary outcome (section 4.2), secondary outcomes (section 4.3) and cervical cancer screening process variables (section 5) will be described separately for each study arm. No formal between-arm comparisons will be performed for these variables; descriptive statistics are presented to characterize the screening cascade and support interpretation of the primary outcome. Results will be reported in a table like Table 3.

10.4. Methodological analyses

10.4.1. Intraclass correlation coefficient

The ICC will be estimated from the random-intercept generalized linear mixed model fitted for the primary analysis, using the standard formula for binomial GLMMs[5]. The 95% confidence interval will be obtained by parametric bootstrap with 2,000 resamples.

10.4.2. Empirical design parameters for future trial planning

Rather than performing a post-hoc power calculation (which is mathematically redundant with the observed p-value and discouraged by current methodological guidance[6]), the trial will report the empirical parameters needed to plan future cluster-randomized trials in similar settings:

- the observed ICC for the primary outcome with 95% CI (section 10.4.1);
- the between-cluster coefficient of variation (k) of the observed cluster-level proportions, by arm;
- the achieved cluster sizes (mean, standard deviation, range, coefficient of variation).

These parameters allow other investigators to recompute prospective power for their own planned trials using standard sample-size formula for cluster-randomized trials[4].

10.5. Missing data

Missing data is not possible for secondary outcome HPV primary screening. The denominator is registry-based and the numerator is ascertained from the trial database; women absent from the database are classified as non-events by definition, as well as women who obtained an invalid HPV test result and did not return for repeat sampling.

For the primary outcome (complete screening) and for the secondary outcomes triage and immediate treatment, HPV-positive women confirmed as not having returned for triage beyond the 6-month follow-up window are classified as not having completed triage. Triage-positive women confirmed as not having received treatment are classified as not having completed immediate treatment. Confirmation requires verification; in the absence of such verification, an unfilled triage or treatment variable is treated as missing rather than as a negative outcome. Women with an invalid HPV test result are excluded from the

denominators of triage-conditional and treatment-conditional outcomes, as their HPV status is unknown; this exclusion is pre-specified.

Missing values are anticipated for the triage and treatment variables described above, for descriptive variables reported in Table 3 (cytology, histology results, and high-grade lesion classification), and for participant-level characteristics reported in Table 2. In all cases, missing values are reported as a separate category. For Table 2 and Table 3 variables, and for the secondary outcomes triage and treatment, no imputation is performed, consistent with their descriptive or exploratory role. Handling of missing triage status for the primary outcome (complete screening) is addressed in the following sensitivity analyses section.

The only covariate included in the analysis models is age stratum, which is available for all women in both the numerator and the denominator. No missing data is expected for this variable.

10.6. Sensitivity analysis

The primary outcome, complete screening, requires a resolved triage status for HPV-positive women. Women with unresolved triage status are excluded from the denominator of the primary (complete-case) analysis, if such cases occur. As a sensitivity analysis, the primary analysis is repeated with these women reclassified as not having completed triage, and therefore as not having achieved complete screening. This conservative assumption penalizes the intervention arm and provides an upper bound on the potential impact of unresolved missingness on the primary effect estimate. Results from the complete-case and conservative approaches are compared to assess robustness of the primary effect estimate. If no such cases occur, the primary analysis proceeds as pre-specified.

10.7. Statistical software

All analyses will be performed in R version 4.5 or above. The analytical code will be archived alongside the trial database.

9. Tables and figures (reporting templates)

Figure 1. Participant flow diagram

A participant flow diagram will be produced, showing the number of clusters assessed and randomized, the number of eligible women in the registry-based denominator and the number of women completing screening for both arms.

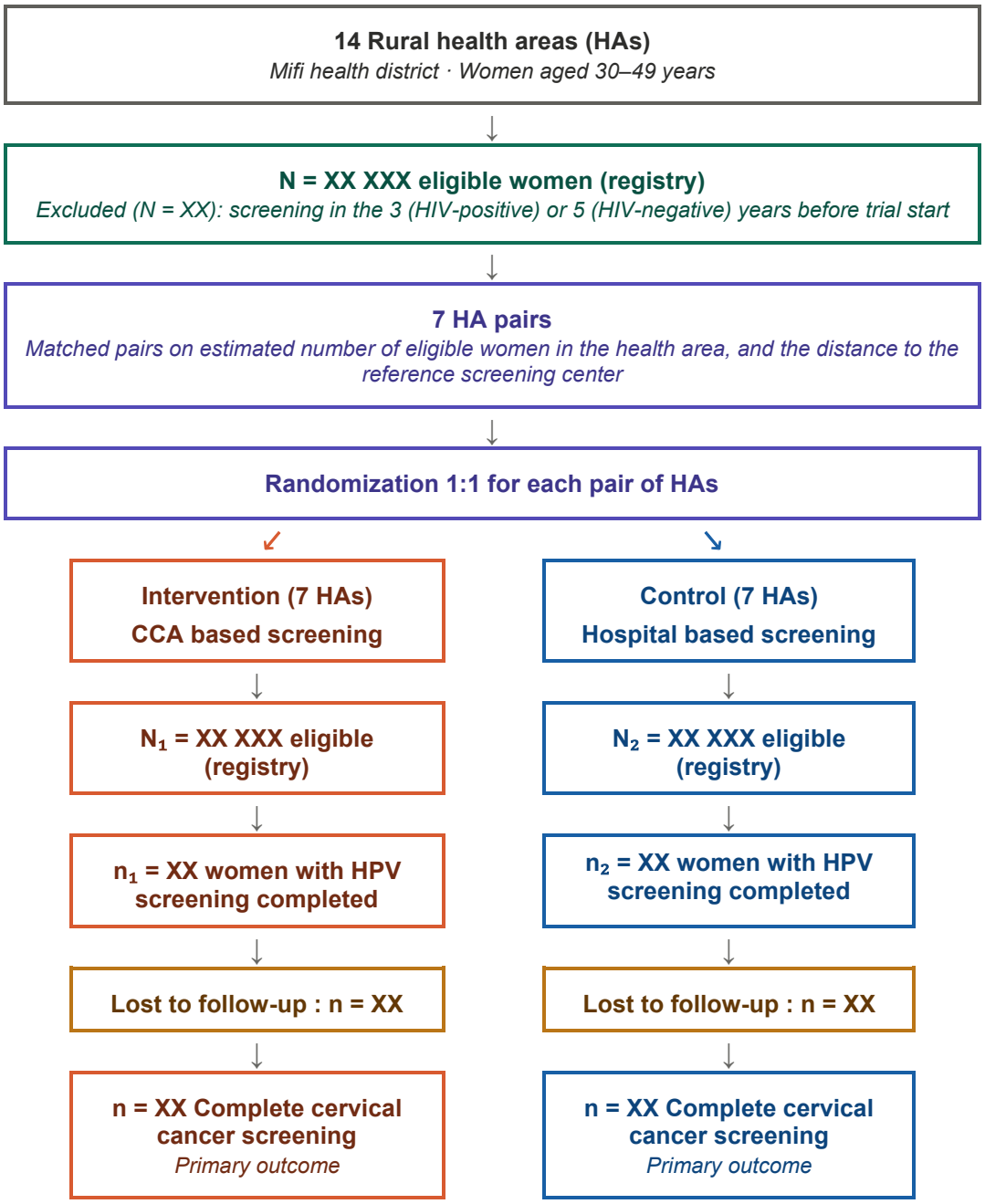


Table 1. Baseline health area characteristics, by arm

Health area characteristics	Control group (n=7)	Intervention group (n=7)
Number of women aged 30-49 years		
Range		
Mean (±SD)		
Number of villages		
Range		
Mean (±SD)		
Number of health facilities		
Range		
Mean (±SD)		
Distance to center (km)		
Range		
Mean (±SD)		
Transportation cost (FCFA)		
Range		
Mean (±SD)		

SD: standard deviation; FCFA: Franc de la Communauté Financière Africaine (national Cameroonian currency).

Table 2. Characteristics of screened participants, by arm

Participant characteristics	Control group (n=) N (%)	Intervention group (n=) N (%)
Age (mean ± SD) (median, Q1Q3, min, max)		
Source of information		
Community health worker		
Word of mouth		
Radio or poster		
Health care worker		
Other		
Missing		
Relationship status		
Single		
In relationship		
Married		
Widow/Divorced		
Missing		
Education level		
No formal		
Primary		
Secondary		
Tertiary		
Other		
Missing		
Occupation		
Housewife		
Agricultural worker		
Salaried without responsibilities		
Salaried with responsibilities		

Participant characteristics	Control group (n=) N (%)	Intervention group (n=) N (%)
Freelance		
Other		
Missing		
HIV status		
Positive		
Negative		
Unknown		
Contraception use		
Yes		
No		
Missing		
Tobacco use		
Yes		
No		
Missing		
Parity (mean ± SD) (median, Q1Q3, min, max)		
Number of lifetime sexual partners (mean ± SD) (median, Q1Q3, min, max)		
Age at first sexual intercourse (mean ± SD) (median, Q1Q3, min, max)		
Sexual intercourse in past 12 months		
Yes		
No		
Missing		

SD: standard deviation; HIV: human immunodeficiency virus; IQR: interquartile range; CC: cervical cancer.

Table 3. Description of cervical cancer screening process and results, by arm

	Control group (n=) N (%)	Intervention group (n=) N (%)
HPV primary screening* (n=)		
Yes		
No		
HPV test result[1] (n=)		
Positive		
Negative		
Non-valid		
HPV genotype[2] (n=)		
Group 1a		
Group 1b		
Group 1c		
Group 1d+		
Multiple genotypes		
Triage completed[3] (n=)		
Yes		
No		
Missing		
Complete screening*[4] (n=)		
Yes		
No		
Missing		
Triage results[5] (n=)		
Negative		
Positive		

	Control group (n=) N (%)	Intervention group (n=) N (%)
Missing		
Cytology results[5] (n=)		
No dysplasia		
ASC-US		
LSIL		
HSIL		
ASC-H		
AGC		
Cancer		
Not valid		
Missing		
Histology results[5] (n=)		
No dysplasia		
CIN1		
CIN2		
CIN3		
Cancer		
Not valid		
Missing		
High-grade lesion[5,6] (n=)		
No		
Yes		
Missing		
Immediate treatment[7] (n=)		
No		

	Control group (n=) N (%)	Intervention group (n=) N (%)
Yes		
Missing		

HPV: Human papillomavirus; ASC-US: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells: cannot exclude HSIL; AGC: atypical glandular cells; CIN1/2/3: cervical intraepithelial neoplasia of grade 1, 2 or 3.

** Denominator: estimated eligible population for screening (women aged 30–49 years from census data, after subtracting those previously screened).*

[1] Among women who completed HPV self-sampling.

[2] Among HPV-positive women. Group 1a: HPV 16; group 1b: HPV 18 and/or 45; group 1c: HPV 31, 33, 35, 52 and/or 58; group 1d+: HPV 51, 59, 39, 56, 66 and/or 68.

[3] Within six months of HPV self-sampling, among HPV-positive women.

[4] Defined as HPV-negative or HPV-positive result with triage completed.

[5] Among women with triage completed.

[6] High-grade lesion is defined as either cervical intraepithelial neoplasia grade 2 or worse (CIN2+) on histology, or high-grade squamous intraepithelial lesion (HSIL) or cancer on cytology.

[7] Among women with triage result positive. Reasons for non-immediate treatment may include large lesions ineligible for thermal ablation (n=x), suspicion of cervical cancer (n=x), technical issues (n=x), and participant refusal (n=x).

Table 4.

	Risk in intervention group (95% CI)	Risk in control group (95% CI)	Risk Difference (95% CI)	RR (95% CI)	p-value
Primary outcome					
Complete screening[1]					
Secondary outcomes					
HPV primary screening[2]					
Triage completed[3]					
Immediate treatment[4]					

RR: risk ratio; CI: confidence interval.

[1] Defined as HPV-negative or HPV-positive result with triage completed.

[2] Within 12 months of trial t0.

[3] Within 6 months of HPV self-sampling, among HPV-positive women.

[4] Among women with a positive triage result.

10. Supplementary material

Table S1. Screening outcomes at health area level

Health area pair	Intervention arm						Control arm					
	Estimated eligible women*	HPV self-sampling N(%)	HPV-positive N(%)[1]	Non-valid result N(%)[1]	HPV+ with triage N(%)[2]	Complete screening[3] N(%)	Estimated eligible women*	HPV self-sampling N(%)	HPV-positive N(%)[1]	Non-valid result N(%)[1]	HPV+ with triage N(%)[2]	Complete screening[3] N(%)
1												
2												
3												
4												
5												
6												
7												
Total												

** Total population eligible for screening estimated based on census data at health area level for women aged 30–49 y.o., after subtracting previously screened women.*

[1] Percentages calculated among all participants who have performed HPV self-sampling.

[2] Percentages calculated among all participants with a positive HPV result.

[3] Includes participants who are either HPV-negative, or HPV-positive and have attended the triage visit.

Table S2. Number of eligible women screened prior to trial start by health area

Health area pairs	Intervention arm			Control arm		
	Nb screened[1]	Estimated eligible women[2]	% Target population screened	Nb screened[1]	Estimated eligible women[2]	% Target population screened
1						
2						
3						
4						
5						
6						
7						
Total						

[1] *Number of screened women based on study data from a previous trial in the same health district.*

[2] *Total population eligible for screening estimated based on census data at health area level for women aged 30–49 y.o.*

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