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Study protocol of the ACCESS trial: a randomised trial to evaluate the effectiveness of human papillomavirus testing by self-sampling in cervical cancer screening uptake and precancer detection

Misuzu Fujita ,[1,2] Minobu Shimazu,[3] Kengo Nagashima ,[4] Misae Suzuki,[5] Ichiro Tauchi,[5] Miwa Sakuma,[5] Setsuko Yamamoto,[5] Makio Shozu,[6] Hideki Hanaoka,[3] Nobuhide Tsuruoka,[7] Tokuzo Kasai,[1] Akira Hata[1,8]

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For numbered affiliations see end of article.

Correspondence to
Dr Akira Hata;
ahata@faculty.chiba-u.jp

ABSTRACT

Introduction Recently, the incidence of cervical cancer has increased in Japan, probably because of an interruption in human papillomavirus (HPV) vaccination and a low cervical cancer screening rate. There is a lack of evidence for self-sampling HPV testing as a cervical cancer screening tool in Japan. The Accelerating Cervical Cancer Elimination by Self-Sampling test trial aims to compare the effectiveness of screening using the self-sampling HPV test with that of routine screening concerning screening uptake and precancer detection.

Methods and analysis This trial has a single-municipality, open-label, parallel, superiority and randomised design. Approximately 20 000 women who have not undergone cervical cancer screening for at least 3 years will be assigned randomly to the self-sampling arm and the control arm using a 1:1 ratio. Participants assigned to the control arm will undergo routine cervical cancer screening (cytology test) provided by Ichihara City, while those assigned to the self-sampling arm will choose the routine screening or self-sampling HPV test. HPV tests will be performed using the cobas 8800 system (Roche Diagnostics, Rotkreuz, Switzerland). Participants who will undergo the self-sampling HPV testing will be recommended to undergo routine screening. The results of the cytology test and further tests, such as colposcopy and biopsy, will be collected and used for this trial. The risk ratio and risk difference in the proportion of participants with cervical intraepithelial neoplasia two or worse between the two arms will be calculated. The test for the null hypothesis (the detection rates are equal between the two arms) will be performed using Pearson's χ^2 test.

Ethics and dissemination This trial was approved by the Research Ethics Committees of the Chiba Foundation for Health Promotion and Disease Prevention and the collaborating research institutes. The results will be disseminated through peer-reviewed journals and conference presentations.

Trial registration number jRCT1030200276. Pre-results.

Strengths and limitations of this study

- This is the first randomised controlled trial to evaluate and compare the effectiveness of cervical cancer screening with self-sampling human papillomavirus (HPV) testing for non-responders to that of routine screening using real-world data in Japan.
- This trial will clarify whether screening using self-sampling HPV testing detects more cervical intraepithelial neoplasia 2 or worse than routine screening.
- This trial will provide suggestions about cervical cancer screening methods in Japan, regardless of whether the result is positive or negative, since it will use the most robust methodology.
- Analyses aimed toward implementation (eg, the participation rate of detailed tests, such as colposcopy and biopsy) and a questionnaire survey of the acceptance of screening using self-sampling HPV testing will also be performed.
- Generalisability might be limited because the participants of this trial are women living in one municipality in Japan.

INTRODUCTION

The predominant cause of cervical cancer is certain types of human papillomavirus (HPV) infection. Therefore, the best approach toward the prevention of HPV-caused cancer is by vaccination and screening.[1]

In Japan, the publicly funded HPV vaccination programme began in December 2010 for girls aged 12–16 years. However, in June 2013, the Ministry of Health, Labour, and Welfare suspended an active HPV vaccine recommendation due to reported adverse events. Thereafter, the vaccination rate in Japan decreased dramatically to almost 0% in 2015.[2] Although

preventive strategies for cervical cancer strongly depend on screening, the rate is extremely low in developed countries that are members of the Organisation for Economic Co-operation and Development, including Japan.[3] These situations have increased the rates of mortality and morbidity due to cervical cancer,[4 5] especially among young women.[5] In 2014, a total of 10 490 cervical cancers were diagnosed in Japan, and there were 2790 cervical cancer-related deaths in 2017. The rates in the future are estimated to increase further.[6] To prevent cervical cancer, effective screening systems to improve the screening rate are urgently required and should be implemented.

Unlike cervical cytology, the HPV test with a self-collected sample has a similar validity as that of a doctor-collected one.[7 8] The sensitivity and specificity of the self-sampling HPV test to detect cervical intraepithelial neoplasia (CIN) two or worse are reportedly 92.9% and 93.9%, respectively.[7] The main reasons for women not opting to undergo cervical cancer screening are: 'a cytology test by a doctor is too embarrassing' or 'it is difficult to find time to undergo a cytology test.'[9–11] Self-sampling might be an alternative method to solve these issues in non-responders to screening. Indeed, previous studies conducted in the USA,[12] Sweden,[13] the Netherlands,[14 15] Denmark[16] and France[17] reported that the self-sampling HPV test increased the participation rate among non-responders, and the test is already implemented in some countries as an option for non-responders.[18 19] However, the current guidelines for cervical cancer screening in Japan do not yet recommend self-sampling HPV testing because of the lack of evidence for the test in Japan. The Japan Society of Obstetrics and Gynecology stated in 2019 that the society does not recommend self-sampling HPV test. Furthermore, they claimed that one of the requirements for approval of the self-sampling test would be to present concrete evidence in Japan, derived from studies that evaluate not only screening uptake, but also the consultation rate of detailed tests, such as colposcopy and biopsy. Thus, to implement a self-sampling HPV test in Japan, the effectiveness of the test should be evaluated using the most robust study design, a randomised controlled trial, in a real-world population.

The main objective of the Accelerating Cervical Cancer Elimination by Self-Sampling test trial is to evaluate and compare the effectiveness of screening with a self-sampling HPV test with that of routine screening in terms of screening uptake and precancer detection in Japan.

METHODS AND ANALYSIS

Study design

This is a single-municipality, open-label, parallel, superiority, randomised trial. Details are shown in the study protocol (online supplemental file 1).

Eligibility criteria and randomisation

Outlines of this trial and time schedule plan are shown in figures 1 and 2, respectively. The trial participants are women who lived in Ichihara City, Chiba Prefecture, Japan. The candidates for this trial will be selected from the database maintained by the Ichihara City Hall as of 22 December 2020, according to the following inclusion criteria:

- Women who lived in Ichihara City on 22 December 2020.
- Women aged between 30 and 59 years as of 1 April 2021.
- Target population for cervical cancer screening in Ichihara City in 2021 (women with an even number of age).
- Women who had not undergone routine cervical cancer screening in Ichihara City for 3 years or more.

Women with an incorrect address will be excluded. Other exclusion criteria will not be used, given the unavailability of relevant data in the database, such as marital status, sexual activity, and pregnant or lactating. Each participant's data administered by the city, including name, address, birthday, and latest year they underwent cervical cancer screening, will be provided to the Chiba Foundation for Health Promotion and Disease Prevention (hereafter, the Foundation), where data management for this trial will be carried out. On 23 December 2020, the inclusion criteria for each candidate will be confirmed, and the candidates for this trial will be registered. On 1 February 2021, we will send a preinvitation letter to all candidates who meet the inclusion criteria, which indicates that they can refuse to participate in this trial (opting out), as shown in online supplemental file 2. Moreover, the objectives and methods of this trial will be publicly available in a public relations newsletter from Ichihara City, a website of the city, and a website of the Foundation on the same day the preinvitation letter will be sent. On 22 February 2021, women whose preinvitation letter returned due to incorrect address or women who opted out by 19 February 2021, will be excluded from the trial. The remaining women will be enrolled in this trial and randomly assigned to the self-sampling arm and the control arm using a 1:1 ratio, according to computer-generated random numbers. All procedures of assignment will be performed at the Foundation at once (central randomisation). The participants who will be assigned to the self-sampling arm will be informed in the second invitation letter. Meanwhile, the participants who will be assigned to the control arm will not receive any information regarding this trial after assignment, which will be stated in the pre-invitation letter. It will not be possible to blind the assignment to participants and screening providers (researchers) due to the nature of the intervention.

Procedures in each arm

Control arm

The city offers routine cervical cancer screening, cytology tests, every 2 years to women aged 20 years or more living in the city. In the fiscal year 2021 (between 1 April 2021 and 31 March 2022), the target population

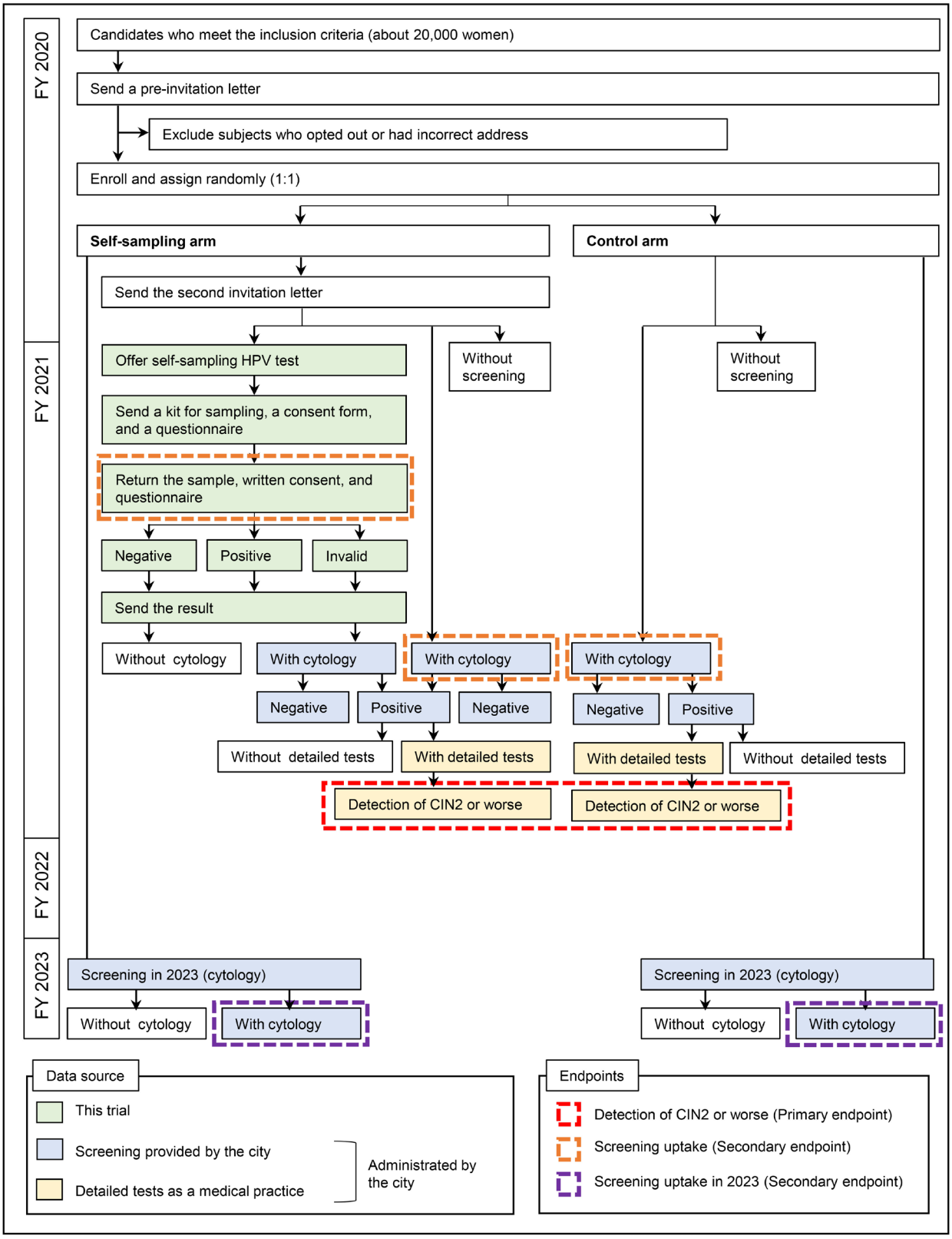

Figure 1 Flow chart of the study protocol. CIN2, cervical intraepithelial neoplasia; HPV, human papillomavirus.

for the screening will include those with an even number of age as of 1 April 2021, which is informed by a public relations newsletter and a website of the city. Additionally, it will be notified that women who underwent a hysterectomy cannot undergo the screening. Since the participants of this trial are a part of the target population for the screening, they can undergo routine screening. Routine screening will be performed at three community centres (on the bus) on 14 and 28 June, 2 and 12 July, 20 October, 10 November, and 3 December 2021,

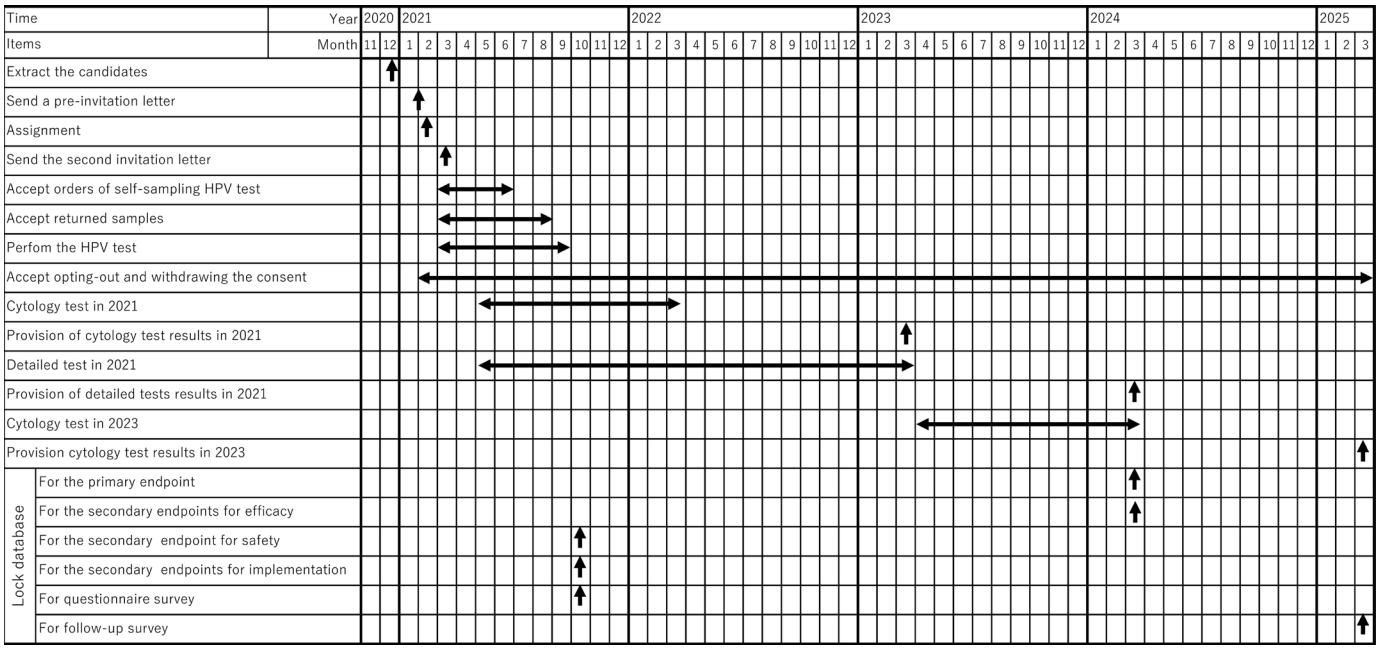

Figure 2 Time schedule plan. HPV, human papillomavirus.

and 17 and 20 January 2022. It will also be performed at the nine clinics in the city between 1 May 2021 and 31 March 2022. A sampling device for cytology tests will not be specified. Liquid-based cytology will be adopted in the screening at the community centres (on the bus) and in one clinic, and a conventional cytology test will be adopted in the remaining eight clinics. If the participants undergo screening at a community centre, the results of the cytology test will be sent from the health centre of the city. In contrast, if they undergo screening at clinics, the result will be reported by the clinic. If the result is atypical squamous cells of undetermined significance (ASC-US) or worse, the participants from health centres or clinics will be referred to some medical institutions for further testing using colposcopy and biopsy. The health centre of the city will collect the results of all cytology tests and almost all detailed tests (87.3% in 2016) and administrate these data. The results of the cytology tests performed between 1 May 2021 and 31 March 2022, will be provided by the city to the Foundation by 31 March 2023, for this trial. The results of detailed tests performed by 31 March 2023, will be provided by 31 March 2024. Additionally, the data of whether the participants undergo cervical cancer screening in the fiscal year 2023 (between 1 April 2023 and 31 March 2024) will be provided by 31 March 2025.

Self-sampling arm

After assignment, the second invitation letter will be sent to the participants assigned to the self-sampling arm on 10 March 2021 (online supplemental file 3). The letter will indicate that they can choose screening with the self-sampling HPV test or routine screening test and how they can order the self-sampling kit, Evalyn Brush (Rovers Medical Devices, Oss, Netherlands). Although previous studies have reported no adverse event related to the use of this kit,[7 8 20] mild vaginal bleeding and pain might occur; however, at a low frequency. Additionally, the letter will inform the participants who have undergone a hysterectomy, are pregnant, and had no sexual experience that they cannot undergo self-sampling HPV testing. A kit order will be accepted by phone or via the website by 30 June 2021. On their orders, a self-sampling kit, an explanatory booklet, an informed consent form (online supplemental file 4), a questionnaire (online supplemental file 5), and an envelope for the sample return with cash on delivery will be sent. The explanatory booklet will provide instructions on how to collect a sample, how to fill the consent form, how to send a sample, the deadline for sending a sample and how to contact for a sample collection-related query. The participants will be asked to collect the sample at home and to return the sample, filled consent form and filled questionnaire. If the informed consent form is not returned to the Foundation, the HPV test and questionnaire survey will not be performed. To send the samples to the laboratory of an outsourced company (LSI Medience, Tokyo, Japan), a staff member of that company will pick up the samples daily. The samples will be stored at room temperature, the condition recommended by the kit manufacturer. The HPV test will be performed using the cobas 8800 system (Roche Diagnostics, Rotkreuz, Switzerland), in which the ß-globin internal cellular control is detected to prevent false negatives. HPV-negative specimens with a negative ß-globin result are flagged as invalid. The frequency of reported invalid results is rare.[12 13 16] When the HPV test result is invalid, the laboratory will perform retest up to two times. The HPV test results, that is positive, negative, or invalid, for each HPV type (type 16, type 18, and other 12 pooled high-risk HPV (hrHPV) including types 31, 33,

35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) will be reported to the Foundation from the laboratory, and we will send the results and cervical cancer screening information in the city to the participants by mail through an outsourced company (Accelight, Tokyo, Japan). For all participants who will undergo self-sampling HPV testing, we will recommend routine cervical cancer screening (cytology test) provided by the city. The messages for informing the participants of their results are shown below: hrHPV-negative: hrHPV was not detected in your sample. Thus, your risk for cervical cancer is thought to be low. However, the possibility of a false negative is not completely excluded. Additionally, the current guidelines for cervical cancer screening in Japan do not yet recommend the self-sampling HPV test. Therefore, we recommend that you undergo the routine cervical cancer screening involving the cytology test. Please carry this result notification along when you undergo the cytology test provided by the city because a doctor may refer to it.

hrHPV-positive: hrHPV was detected in your sample. You have a relatively high risk of developing cervical cancer. If high-risk types 16 and/or 18 were detected, the risk is thought to be higher. Be sure to undergo the routine cervical cancer screening involving the cytology test. Please carry this result notification when you undergo the cytology test provided by the city because a doctor may refer to it.

Procedures for routine screening (cytology test), detailed tests and providing the results will be the same as that for the control arm as mentioned above.

Although we will not give any information to the primary outcome assessors (doctors in the screening institutions), they will not be blinded completely because the participants who will undergo self-sampling HPV testing will carry the HPV test results along. The reason for adopting this strategy is that this procedure is expected to be used if the self-sampling HPV test is recommended as a screening option in future, thus providing real-world evidence.

Time schedule plan

This trial will be performed between 22 December 2020 and 31 March 2025 (figure 2).

- Selection and data extraction of candidates who meet the inclusion criteria: 22 December 2020.
- Registration of the candidates who meet the inclusion criteria: 23 December 2020.
- Sending a preinvitation letter: 1 February 2021.
- Enrolment and assignment: 22 February 2021.
- Sending the second invitation letter to the participants assigned to the self-sampling arm: 10 March 2021.
- Accepting orders for the self-sampling test: By 30 June 2021.
- Accepting samples from the participants: By 31 August 2021.
- Performing the HPV test: By 30 September 2021.
- Accepting opt-out and withdrawal of consent: By 31 March 2025.
- Cervical cancer screening in 2021 (cytology test): Between 1 May 2021 and 31 March 2022.
- Detailed tests based on the results of the cytology test in 2021: By 31 March 2023.
- Cervical cancer screening in 2023 (cytology test): Between 1 April 2023 and 31 March 2024.
- Database lock.
  - Analyses of the primary and secondary outcomes for effectiveness: By 31 March 2024, including 'proportion of cytology tests performed.'
  - Analysis for safety, implementation and questionnaire survey: By 31 October 2021, except for 'proportion of cytology tests performed.'
  - Analysis for follow-up survey (screening uptake in 2023): By 31 March 2025.

Endpoints

Primary endpoint

The primary endpoint is the detection of CIN2 or worse determined by detailed tests (biopsy) conducted by 31 March 2023. CIN2 or worse will be included in the following situations:

- CIN2.
- CIN3.
- Adenocarcinoma in situ.
- Squamous cell carcinoma (SCC: including microinvasive and invasive SCC).
- Adenocarcinoma (including microinvasive and invasive adenocarcinoma).
- Adenosquamous carcinoma.
- Other cervical primary cancer.
- Metastatic cancer in the cervix.

Secondary endpoints for effectiveness

- Screening uptake.
- Participants who have received the cytology test.
- Participants who required detailed tests.
- Participants who have received detailed tests
- Detection of CIN2 or worse per cytology test.
- Positive predictive values.

Detailed definitions will be described in the statistical analysis plan (SAP), as shown in online supplemental file 6.

Secondary endpoint for safety

- Incidence of adverse events.

Detailed definitions will be described in the SAP (online supplemental file 6).

Endpoints aimed toward implementation

- Proportion of self-sampling HPV tests ordered.
- Proportion of self-sampling HPV tests ordered through the website.
- Proportion of self-sampling HPV tests returned.
- Proportion of positive HPV tests.
- Proportion of invalid HPV tests.
- Proportion of cytology tests received.

- Time to each event.
  - Time to ordering of self-sampling HPV tests.
  - Time to sending of self-sampling kits to the participants.
  - Time to return of self-sampling kits by the participants.
  - Time to ordering of HPV test to the laboratory.
  - Time to return of HPV test results by the laboratory.
  - Time to sending of HPV test results to the participants.
  - Total time.

Detailed definitions will be described in the SAP (online supplemental file 6).

Questionnaire survey

- Reasons for not having cervical cancer screening.
- Knowledge about HPV
- Experience of self-sampling HPV test.
- Preference for screening, sampling by a doctor, or self-sampling.

The questionnaire is shown in online supplemental file 5, and detailed definitions will be described in the SAP (online supplemental file 6).

Follow-up survey

In the follow-up survey, screening uptake in 2023 will be compared between the two arms.

Detailed definitions will be described in the SAP (online supplemental file 6).

Sample size calculation

The sample size was calculated based on the primary outcome of detection of CIN2 or worse. According to previous studies, we set the following assumptions:

Self-sampling arm

Among the participants in the self-sampling arm, the proportion of those who will undergo self-sampling HPV testing (A): 0.13.[13 16 21–24]

In A, the proportion of HPV-positive participants (B): 0.117.[25]

In B, the proportion of participants who will undergo cytology testing (C): 0.79.[14–17 21 26–29]

In C, the proportion of participants whose cytology test result is ASC-US or worse (D): 0.18.[25 30]

In D, the proportion of participants who will undergo detailed testing (E): 0.99.[14 15 28 29]

In E, the proportion of participants detected as CIN2 or worse (F): 0.54.[14 15 28 31 32]

Among the participants in the self-sampling arm, the proportion of those who will undergo cytology testing without self-sampling HPV testing (G): 0.03.[10 13 28 33]

In G, the proportion of participants whose cytology test result is ASC-US or worse (H): 0.03.[25 30]

In H, the proportion of participants who will undergo detailed testing (I): 0.74.[12 28 29 34 35]

In I, the proportion of participants detected as CIN2 or worse (J): 0.34.[12 28 29 31 32 34–36]

Control arm

- Among the participants in the control arm, the proportion of those who will undergo cytology test (K): 0.03.[10 13 28 33]
- In K, the proportion of participants whose cytology test result is ASC-US or worse (L): 0.03.[25 30]
- In L, the proportion of participants who will undergo detailed testing (M): 0.74.[12 28 29 34 35]
- In M, the proportion of the participants detected with CIN2 or worse lesions (N): 0.34.[12 28 29 31 32 34–36]

Based on these assumptions, the detection rate of CIN2 or worse lesions in each arm is calculated as follows:

Self-sampling arm: A*B*C*D*E*F+G*H*I*J=0.001156+0.000226=0.00138

Control arm: K*L*M*N=0.00023

To detect the difference in the rate between the two arms under a two-sided alpha of 0.05 and power of 0.80, the calculated sample size is 19 094. We assumed that 5% of women will refuse to participate in the trial (opting out) or have an incorrect address. Finally, the sample size should be approximately 20 000 (10 000 in each arm).

The population of women in Ichihara City aged between 30 and 59 years as of 1 October 2020, was 48 945. Since the city provides cervical cancer screening to only women with an even number of age, we divided the population by two (48,945/2=24 473). According to the Report on Regional Public Health Services and Health Promotion Services in 2018, the proportion of women who did not undergo cervical cancer screening for at least 2 years was 84%. Thus, we multiplied the remaining number by 0.84 (24 473×0.84=20 557). We estimated that 20 557 women would meet the inclusion criteria of this trial.

Population to be analysed

Intention to screen

Intention to screen (ITS) will include all participants who are randomised, excluding those who will opt out after randomisation and those who withdraw their written consent.

Modified ITS

Modified ITS (mITS) will include all participants who are randomised, excluding those who will opt out after randomisation and those who will withdraw their written consent. However, in the endpoints, cytology tests and detailed tests in HPV-negative participants will not be included.

Per protocol

Per protocol (PP) will include all participants in the self-sampling arm who will undergo self-sampling HPV testing or cytology testing and the participants in the control arm who will undergo cytology testing. However, in the endpoints, cytology tests and detailed tests in HPV-negative participants will not be included.

Other population to be analysed

Details will be described in the SAP (online supplemental file 6).

Analysis plan

Primary endpoint analysis plan

The frequency and percentage with 95% CI will be calculated for each arm. The risk ratio and risk difference in the percentages of participants detected with CIN2 or worse between the two arms (risk ratio=percentage of participants detected with CIN2 or worse in the self-sampling arm/that in the control arm; risk difference=percentage of participants detected with CIN2 or worse in the self-sampling arm—that in the control arm) and the 95% CI will be calculated. The test for the null hypothesis (the detection rate of CIN2 or worse is equal among the two arms) will be performed using Pearson's χ^2 test. As necessary, sensitivity analyses using the Mantel-Haenszel test adjusted for the time period since the last screening (3–5 years, 6 years or more, those without a history) and age category (30–39 years, 40–49 years, 50–59 years) will also be performed.

ITS will be used in the primary analysis as a population to be analysed. As necessary, sensitivity analyses will be performed using mITS and PP.

Other analysis plan

Details will be described in the SAP (online supplemental file 6).

Patient and public involvement statement

The general population and women living in Ichihara City were not involved in preparing the study protocol, registration of participants and conducting the trial.

ETHICS AND DISSEMINATION

Ethical considerations

To ensure autonomous participation and reduction of selection bias as much as possible, opt-out consent will be obtained from all participants. In detail, we will send a preinvitation letter to all women who meet the inclusion criteria, with the option to opt out. Additionally, we will obtain written consent from the participants who undergo self-sampling HPV testing. The procedure complies with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. This trial was approved by the Research Ethics Committees of the Chiba Foundation for Health Promotion and Disease Prevention (approval number R2-2), Graduate School of Medicine, Chiba University (approval number 3979) and Institute of Statistical Mathematics (approval number ISM20-001). Since Ichihara City does not have an ethics committee, the Committee of the Chiba Foundation for Health Promotion and Disease Prevention reviewed the protocol instead of Ichihara City (approval number R2-7).

For this trial, Ichihara City provided the existing data to the Foundation. Before the provision, the Committee for Personal Information Protection of Ichihara City reviewed the plan of this trial on 12 November 2020, and authorised data provision on 15 December 2020. Considering this approval, the city was allowed to provide existing data and to launch this trial.

Data sharing

We will not share any data of this trial following the opinions of the Committee for Personal Information Protection of Ichihara City.

Publication of the results

The results from this trial will be disseminated through peer-reviewed journals and conference presentations after protecting the human rights of the subjects and their related parties and managing the interests of researchers and related parties. According to the statement from the International Committee of Medical Journal Editors, the authors will be determined.

Author affiliations
[1]Department of Health Research, Chiba Foundation for Health Promotion and Disease Prevention, Chiba, Japan
[2]Department of Public Health, Chiba University Graduate School of Medicine, Chiba, Japan
[3]Clinical Research Center, Chiba University Hospital, Chiba, Japan
[4]Research Center for Medical and Health Data Science, The Institute of Statistical Mathematics, Tachikawa, Tokyo, Japan
[5]Municipal Health Center, Department of Health and Welfare, Ichihara City, Ichihara, Japan
[6]Department of Reproductive Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
[7]Yushudai Clinic, Ichihara, Chiba, Japan
[8]Center for Preventive Medical Sciences, Chiba University, Chiba, Japan

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ORCID iDs
Misuzu Fujita http://orcid.org/0000-0001-5308-4744
Kengo Nagashima http://orcid.org/0000-0003-4529-9045

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