Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Market Consultation

Cervical cancer screening

Consultation of the market on technical possibilities for the optimization of the Dutch cervical cancer screening program

Tendernumber 243224

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1 Preface

1.1 General information

RIVM
The National Institute for Public Health and the Environment (RIVM) is an agency of the Ministry of Health, Welfare and Sport (VWS) and carries out its duties for policy development and monitoring in the areas of public health, the environment and nature. The RIVM consists of thirty components, mainly laboratories, teams or centers with a specific research task. These components, all based in Bilthoven, have been placed in three knowledge domains: Infectious Diseases and Vaccinology, Environment and Safety and Public Health and Care.

The Center for Population Screening (hereafter: RIVM-CvB) is placed under the Public Health and Care domain. RIVM-CvB has been commissioned by the Ministry of Health, Welfare and Sport and is responsible for overseeing the Dutch population screening programs. This concerns the population screening for cervical cancer, breast cancer, colon cancer and pre- and neonatal screening programs. The RIVM-CvB is therefore responsible for developments within a program and sets frameworks for tenders. For more information about the Center for Population Screening: https://www.rivm.nl/rivm/organisatie/centrum-voor-bevolkingsonderzoek.

FSB
Five screening organizations organize and coordinate the screening of cancer in their region on behalf of the RIVM-CvB within the national frameworks. The screening organizations are contracting authorities and conclude agreements with suppliers laboratories of the cervical cancer screening program. The five screenings organizations have organised their facility services in a co-operation. This co-operation is Facilitaire Samenwerking Bevolkingsonderzoeken (hereafter: FSB). For more information about the screening organizations: https://www.bevolkingsonderzoeknederland.nl.

Project team
This market consultation was prepared by a project team consisting of RIVM-CvB and FSB. RIVM-CvB participates in the project team in its role as responsible for any adjustments to the structure of the population screening program. Since this is closely linked to opportunities that market parties can offer, and FSB is responsible for tendering and managing agreements with market parties, a team consisting of both organizations has been chosen. RIVM-CvB is responsible for this market consultation. Where it concerns the conduct of the market consultation in this document, the project team will be referred to.

1.2 Reason for the market consultation

At the start of 2017 primary HPV screening was introduced in the Dutch cervical cancer screening program, with cytology as triage. In addition, a self-sampling device has been introduced for women who find it difficult to have a pap smear made. RIVM-CvB has the wish to further optimize this population screening program. Foreseen developments are the influx of HPV vaccinated women in 2023, the reduction of the number of unnecessary referrals and a strengthening of the use of the self-sampling device. More background information is given in chapter 2.

For the purpose of conducting the screening test, agreements have been concluded with suppliers of the HPV test and the self-sampling device. As a result of the expiry of these agreements, new agreements must be concluded by FSB in the near future. The foreseen developments within the population screening must be taken into account. The possible scenarios and strategies are currently being worked out.

The project team attaches great importance to the knowledge of market parties and wants to consult them about the technical possibilities for optimization that are or will become available. An open market consultation is therefore held for additional information to describe the scenarios and strategies

In the market consultation, parties are asked for information that can help with the preparations for an optimization of the cervical cancer screening program. The information and knowledge that is collected can also contribute to the drafting of a procurement strategy.

This document describes the manner in which RIVM-CvB carries out this market consultation and which conditions apply (hereafter: the market consultation document). Parties are free to participate (or not) in this market consultation. Participation in this market consultation is not a condition for being able to participate in future tenders. Whether or not to participate in this market consultation has no influence on the position of parties in future tenders.

1.3 Objective of the market consultation

The goal of this market consultation is to gain a better understanding of market developments and also to obtain answers to specific questions. In this way, RIVM-CvB wants to get a realistic picture of the possibilities to optimize the cervical cancer screening program.

With this market consultation, the project team aims to:

a. reach, interest and stimulate as many parties as possible to think along
b. gain insight into possible solutions and the way in which parties can contribute to this
c. test our own principles and assumptions
d. gather input for describing scenarios and drafting of a procurement strategy
e. gain insight into potential market parties

1.4 Structure of the market consultation

The market consultation consists of the following process steps.

1. Publishing. The market consultation document has been published on TenderNed and is therefore accessible to everyone.
2. Information notice. Market parties can ask RIVM-CvB questions about the procedure of the market consultation and the questions that the project team has for the market. RIVM-CvB will make the answers to these questions known by publishing an information notice on TenderNed.
3. Questionnaire. The RIVM has a number of questions to the market. Market parties are able to answer these by submitting a completed questionnaire. We call this part 1 of the market consultation.
4. Consultations. Following the submitted questionnaires, RIVM invites a number of market parties to deepen the relevant topics in an interview. We call this part 2 of the market consultation.

The process steps are further explained in chapters 3-5 of the market consultation document.

RIVM-CvB invites market parties with insight into technical developments that can contribute to the optimization of the cervical cancer screening program to participate in this market consultation. We primarily think of suppliers of collection devices, analysis methods and laboratory equipment in the field of cervical cancer screening. In addition, other parties that can make a meaningful contribution are certainly also invited to participate in this market consultation. Naturally, the principles of transparency, equality and non-discrimination are taken into account in this market consultation with a view to possible future tenders.

2 Background information

2.1 Population screening for cervical cancer

Cervical cancer screening program
The Dutch population screening for cervical cancer is a preventive screening program that is offered by the government to women between 30 and 60 years old. Cervical smears were collected and used for diagnostics and screening on a large scale in the Netherlands since 1970. Since 1996 a nationally standardized population based screening program has been applied, based on cytological screening of cervical smears, collected at 5 years intervals on a voluntary basis from women between 30 and 60 years of age

In January 2017, the cervical cancer screening program was renewed by introducing high risk HPV detection in primary screening on GP collected cervical smears, followed by cytology as a triage in hrHPV positive women. If abnormal cells are observed upon cytological assessment (ASCUS+), the woman is being referred to a gynecologist . If no abnormal cells are observed, the woman is advised to have a new smear taken after 6 months for a new cytological assessment. If abnormal cells are detected in the in the control smear (ASCUS+), the woman is being referred to a gynecologist.

In addition, a self-sampling device has been introduced for women who find it difficult to have a cervical smear taken at the GP. With this device, the woman can obtain a sample for hrHPV screening herself and send it to the laboratory by regular mail. No cytological assessment can be performed on this material. If the self-collected sample is hrHPV positive a regular cervical smear needs to be taken by a GP for subsequent cytological evaluation.

If the primary screening result for either the regular cervical smear or the self-collected sample was negative for the detection of hrHPV, no further follow up is required until the next screening round For women of 30, 35, 45 or 55 years old, the next round will be after 5 years, whereas for hrHPV negative women aged 40 or 50 the next round will be after 10 years. Women who are hrHPV positive will in all cases receive a new invitation after 5 years, independent of age.

Objective en target group
The aim of the cervical cancer screening program is to reduce mortality by detecting the early stages of cervical cancer and preventing the development of cervical cancer.

The screening program focuses on women aged 30 to 60 years. Around 800 women are diagnosed with cervical cancer in the Netherlands each year, especially between the ages of 30 and 60. Approximately 200 women die from cervical cancer each year.

Size of the program
Currently, approximately 450,000 smears and 30,000 self-samples are analyzed annually as part of national cervical cancer screening program. In 9.5% of the participants hrHPV is detected, which translates to almost 14,000 women who are being referred to the gynecologist. In around 5000 of the referrals a preliminary stage of cervical cancer (CIN2+) is found.

Laboratory screening
HPV analysis and cytology are performed according to standardized methods, procedures and equipment in 5 screening laboratories. The hrHPV screening is performed with a clinically validated DNA PCR test. The hrHPV test is part of an automated sample-in result-out solution consisting of the necessary equipment, reagents, disposables and control materials to screen for the presence of hrHPV DNA in cervical samples.

The self-sampling device has been proven to be compatible and suitable with the hrHPV screening assay applied in the national cervical cancer screening program. Self-samples are processed in the same medium and volume as smears. The pre-analytic processing of self-sampling devices includes the following (manual) steps: barcode scanning, printing and labelling, decapping of the medium vial, transferring brush from device to vial, recapping and vortexing of the medium vial. Individual

self-samples are processed sequentially to minimize the risk of sample mix-ups. Cytology triage and control examinations after 6 months are performed using thin layer cytology.

2.2 Optimization of the screening program

RIVM-CvB wishes to further optimize the cervical cancer screening program, to accommodate for the influx of HPV vaccinated women, for the reduction of the number of unnecessary referrals and for the strengthening of the use of the self-sampling device. Strengthening the use of the self-sampling device is a wish, because this is expected to result in a more accessible program. However, repositioning the use of the self-sampling device is a substantial change to the screening program, in particular because, of the significant increase in the number of self-samples that needs to be processed by the laboratories and the fact that this processing currently involves multiple manual steps. The three foreseen developments are briefly explained below.

Influx of HPV vaccinated women

In 2009, HPV vaccination of girls started in the Netherlands. This first group involved a catch-up of girls from 13 to 16 years old. From 2010 HPV vaccination has been introduced for 13-year-old girls. In 2023, the first girls who received an invitation for HPV vaccination will turn age 30 and become eligible for an invitation to attend the national cervical cancer screening program.

The coverage rate for vaccination varies over the years and declined in recent years. Currently, about 50% of the girls receive the bivalent (HPV16 and HPV18) vaccine.

RIVM-CvB has started a project to investigate the consequences of the influx of vaccinated women for the screening program and to prepare for the necessary adjustments.

Reduction of unnecessary referrals

Based on the current screening algorithm (HPV positive ánd ASCUS+ → referral to gynecologist), more than 50% of the screened women are being referred to the gynecologist without cervical abnormalities (CIN2+). Thus, the referral was unnecessary in these women and resulted in false positivity. A false positive result is a negative experience for a women, since she may become unnecessarily worried, undergoes unnecessary follow-up with the risk of over treatment. In addition, this high percentage of unnecessary referrals results in an increase of health care costs.

RIVM-CvB is exploring options for reducing the number of unnecessary referrals. The strategy must fit within the screening program and focuses on an improved triage after a positive HPV result. Possible strategies to reduce the number of false positives are:

- optimization of the cytological assessment
- adjusting the screening algorithm
- introduction of an alternative triage method

An alternative strategy should increase the specificity of the triage, without a substantial loss of sensitivity.

Strengthening of the self-sample device

In the screening program, a self-sampling is offered to women who find it difficult to have a cervical smear taken at the GP. Extending the application of self-sampling, offers the possibility of (potentially) increasing the accessibility of the program by reducing the barrier to participation that may be associated with the need to have a cervical smear taken by a GP.

Possible options for a strengthening of the self-sampling device are:

- to send a self-sampling device with the reminder for the screening in women who did not respond to the initial invitation letter
- to offer women at the first invitation the option to choose between self-sampling or cervical smear sampling by their GP
- to send all women a self-sampling device at the first invitation for the screening

By repositioning the self-sampling device, we hope to make it as easy as possible for women to participate in the screening program.

Optimal balance
The Dutch cervical cancer screening program must meet an optimal balance between the public values issued by the government: quality, accessibility and affordability. Insight into what market parties can offer to optimize the program in the short and longer term, helps RIVM-CvB to determine direction. A direction for adjustments to the screening program whereby the balance between the public values are guaranteed as much as possible.

3 Questionnaire (part 1 market consultation)

This consultation, aims to give parties the opportunity to comment on the needs of RIVM-CvB to optimize the cervical cancer screening program. Part 1 of this market consultation consists of a questionnaire with questions to the market, as shown below. The questions presented in this chapter are asked in the context of the preceding sections with regard to the background information and the expected developments within the program.

You are kindly requested to answer the questions below in writing, by using the answer form 'questionnaire' in TenderNed and handing in the pdf document per message with the module 'berichten' in TenderNed. Any business-sensitive information is not disclosed.

Participants in this market consultation can choose to which questions they want to formulate a response, it is not mandatory to answer all questions. The RIVM-CvB does ask participants to provide sufficient substantiation for the questions answered.

There is no restriction to the length and content of the answers. The RIVM-CvB prefers concise and to the point answers.

The questions are asked in a direct sense, which does not exclude you from answering these in general (when you are not a supplier of the product in question). If your product only covers part of the laboratory procedure(s), please indicate this explicitly.

Number	Question
1	In 2023, the first HPV-vaccinated women are eligible to be invited to the cervical cancer screening program. RIVM-CvB must ensure a responsible influx. **Questions:** **a.** To what extent is your HPV test, based on test characteristics, suitable for screening a (partially) vaccinated population and how has this been tested? **b.** Has your HPV test been clinically validated for testing samples of a (partially) vaccinated population and how is that included in the package insert of the test?
2	The current screening algorithm of the program is based on primary HPV screening with cytology triage. All HPV positive women with ASCUS+ are referred to the gynecologist. CIN2 + is considered as a clinically relevant abnormality. **Question:** Which alternative screening algorithms would be possible based on HPV testing with your HPV test (and cytology as triage), whereby specificity increases without a substantial loss of sensitivity?
3	RIVM-CvB is exploring options for reducing the number of unnecessary referrals. **Questions:** **a.** What possibilities do you see (have available), for example in additional methods, to increase the specificity of cytology? **b.** Do you expect that (in the short term) alternative methods will become available for the triage of women after a HPV positive result within a screening setting? If yes, which one(s)?
4	With an increasing use of the self-sampling device within the screening program, it is important that the outcome of the screening result remains guaranteed. **Questions:** **a.** To what extent is your HPV test clinically validated for the use of self-samples and (how) has this been included in the package insert of the tests? **b.** If so, to which combinations of devices and media does the clinical validation apply and what criteria have been applied? **c.** If not, what options do you see for the clinical validation of HPV tests on samples taken with a self-sampling device?

Number	Question
5	Currently hrHPV genotyping is not applied in the Dutch population screening for cervical cancer. For primary HPV screening, however, genotyping of high risk types is becoming increasingly important. **Questions:** **a.** To what extent has your (clinically validated) HPV test the possibility of (partial) genotyping and for which hrHPV types? **b.** How could genotyping (with your HPV test) contribute to the optimization of the Dutch population screening program?
6	No cytology can be performed on samples taken with a self-sampling device. If hrHPV is detected, it is therefore necessary for the woman to have a smear taken for cytological evaluation. This increases the chance of loss-to-follow-up. **Question:** Do you expect methods to become available (on the short term) that will allow HPV analysis and triage both to be performed on the same self-sample? If yes which one(s)?
7	On April the 5th 2017, the European Parliament adopted a regulation for medical devices and a regulation for in vitro diagnostics: the Medical Device Regulations (MDR) and the In Vitro Diagnostic Medical Device Regulations (IVDR). This means that medical devices (self-sampling devices) from May 26th 2020 and in-vitro diagnostics (HPV tests) must comply with new European rules from May 26th 2022. Existing certificates are still valid until May 2024. **Question:** To what extent have you prepared yourself for these new regulations and what is your planning / plan of action?
8	The HPV analysis of collected material (smears and ZAS) takes place in a limited number of screening laboratories. The HPV analysis must contribute to the timelines of the total screening program. **Questions:** **a.** Is your (clinically validated) HPV test suitable for automated high throughput screening with low labor intensity? **b.** What is the capacity in terms of numbers of samples that can be processed per day and what are the assay turnaround times?
9	An important point of attention in increasing the use of the self-sampling device is the processing of larger numbers of samples by the screening laboratories. The current pre-analytical process is labor-intensive and requires many manual actions, thereby increasing the chance of sample mix-ups or contaminations. **Questions:** **a.** What possibilities do you see for (the development of) pre-analytical automation for the processing of self-sampling sets within the screening laboratories? **b.** Do you see possibilities for full tracking and tracing of the sample? **c.** Do you have suggestions for the optimization of self-sampling devices to simplify the pre-analytical processing? **d.** What options do you have / expect for an integrated solution consisting of automated pre-analytical processing of self-samples in combination with a clinically validated HPV screening solution?
10	**Open question:** Do you have any points of interest that you would like to provide to RIVM-CvB to take in account when developing scenarios and strategies for program optimization?

4 Consultations (part 2 market consultation)

The questionnaires completed as part of part 1 of the market consultation are reviewed by the project team that prepared this market consultation. All reactions are treated with the greatest possible care. Based on the responses, the project team will decide with which parties they will conduct bilateral consultations during part 2 of the market consultation.

The parties selected by the project team for the bilateral consultations will receive an invitation for the meeting. The parties also receive prior to the consultations the in-depth questions that RIVM would like to discuss in addition to the already submitted questionnaire. These questions serve as a guide for the consultation. The duration of the consultation is 1.5 hours.

The consultations will be held by members of the project team. The following expertise is represented within the project team:

- Project Manager optimization (RIVM-CvB)
- Academic Staff Member cervical cancer screening (RIVM-CvB)
- Senior Biomedical Scientist(s) (RIVM-CvB)
- Purchasing Strategic Advisor (RIVM-CvB)
- Manager cervical cancer screening (FSB)
- National Reference Officers HPV and Cytology (FSB)
- Staff Member quality assurance screening laboratories (FSB)
- Contract Manager cervical cancer screening (FSB)

5 Process, timeline, terms and conditions, guidelines TenderNed

5.1 Process

This market consultation starts by publishing this market consultation document in TenderNed.

During the information notice (see section 5.2), participants can ask questions about the content and the process of this market consultation in writing. The project team will answer the questions during the period of the information notice and aims to answer the final questions by December 2th 2019 at the latest.

The information notice is followed by a period in which interested market parties can answer the questions from the questionnaire that are included in Chapter 3 of this market consultation document. The closing date for answering the questions is December 13th 2019 at 4 p.m.

Based on the answers to the questionnaire, the project team makes a selection of parties that will be invited for consultation (chapter 4). The consultations will take place in the period from January 20th 2020 to February 7th 2020. The invitations to the consultations will be sent no later than December 20th 2019.

5.2 Information notice

If parties have substantive or procedural questions as a result of part 1 of this market consultation, they can only be asked by using the available 'question form' (excel document) and handing in the excel document with questions per message with the module 'berichten' in TenderNed.

Questions that are submitted other than through the 'question form' (excel document), or that are not submitted in accordance with the following, will not be processed.

Questions for the 'Information note' can be submitted continuously from the time of publication of the market consultation document up to the deadline for submitting questions for the Information notice, namely on November 26th 2019 at 4 p.m.

The project team aims to answer the questions during this period. The Information notice will be published in TenderNed on December 2th 2019.

It is recommended that the answers to the questionnaire as included in Chapter 3 should only be submitted after the Information notice has been completed, since the starting points are only final after publication of the Information notice.

Individual questions

Participants who have the opinion that certain information during the 'Information notice' is not suitable for distribution due to their business-sensitive nature should make this known when they request information. Participants can do this by ticking the individual question option in the 'question form' (excel document). The motive for answering the question individually must be stated by the participant. The question can only be considered as an 'individual question' if disclosure of this information would harm the justified economic interests of the company. RIVM-CvB decides on the basis of the motivation whether it finds the economic interests justified. After answering an individual question, it is only visible to the participant who asked the question.

If RIVM-CvB is of the opinion that the economic interests are not justified, it can ask the participant to ask the question again, without considering it as individual. An individually answered question does not receive a question number, so that other participants are not informed about how many individual questions and answers there are.

5.3 Timetable

The timetable below, provides an overview of the key stages and dates in this market consultation. The project team reserves the right to change these dates as necessary. If the timeline is changed, this will be communicated in time in TenderNed.

Date	Stage
04-11-2019	Publication of market consultation document by pre-announcement on www.tenderned.nl.
26-11-2019, 4 p.m.	Final date and time for asking questions by interested parties for part 1 of the market consultation (Information notice).
04-11-2019 untill 26-11-2019	Answering of questions from interested parties by the project team.
02-12-2019	Publication of the Information notice by RIVM-CvB.
13-12-2019, 4 p.m.	Finale date and time for answering and submitting the answers to the questionnaire by participating market parties.
27-01-2020 untill 07-02-2020	Consultations (bilateral).

5.4 Terms and conditions

Through this market consultation, parties are given the opportunity to respond to RIVM-CvB's question regarding the technical options for optimizing the Dutch cervical cancer screening program

Below are the general terms and conditions that apply to participation in this market consultation. Participants in the market consultation unconditionally agree to these conditions. It concerns the following conditions:

a. This market consultation will be conducted in the English language only.
b. This market consultation is carried out through TenderNed. All communication takes place in TenderNed. The participants cannot derive any rights with regard to this market consultation from verbal statements made by or on behalf of RIVM-CvB.
c. The information made available by RIVM-CvB in the context of this market consultation should only be used for the purpose for which it was provided. It is not permitted to make this information available to third parties or to multiply it for a purpose other than that for which it was provided.
d. Parties cannot derive any rights from the information provided during the market consultation.
e. Participation is free. No costs will be reimbursed for your participation by RIVM-CvB.
f. The results of the market consultation (parts 1 and 2) may be shared in general and anonymously, at the discretion of RIVM-CvB and taking into account any business-sensitive nature of the information.
g. Information provided during the market consultation may differ from information to be provided in future procurement procedures.
h. The project team may use the information obtained from the market consultation at its own discretion in policy advices and in documents for future tenders.

5.5 Guidelines TenderNed

The following website provides guidelines from registering to participating in a market consultation on TenderNed. If you have any question regarding TenderNed you can contact the service desk at +31 (0)70-3798899 or servicedesk@tenderned.nl.