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**Fluorescent indocyanine green versus technetium-99m and blue dye for bilateral SENTinel lymph node detection in stage I-IIA cervical cancer (FluoreSENT): protocol for a non-inferiority study**

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Fluorescent indocyanine green versus technetium-99m and blue dye for bilateral SENTinel lymph node detection in stage I-IIA cervical cancer (FluoreSENT): protocol for a non-inferiority study

**Authors:**

Ilse G.T. Baeten<sup>a</sup> MD, Jacob P. Hoogendam<sup>a</sup> MD PhD, Arthur J.A.T. Braat<sup>b</sup> MD PhD, Wouter B. Veldhuis<sup>b</sup> MD PhD, Geertruida N. Jonges<sup>c</sup> MD PhD, Ina M. Jürgenliemk-Schulz<sup>d</sup> MD PhD, Ronald P. Zweemer<sup>a</sup> MD PhD, Cornelis G. Gerestein<sup>a</sup> MD PhD

<sup>a</sup> Department of Gynaecologic Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>b</sup> Department of Radiology and Nuclear Medicine, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>c</sup> Department of Pathology, Division of Laboratory, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>d</sup> Department of Radiotherapy, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

**Corresponding author:** Ilse G.T. Baeten MD, Department of Gynaecological Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, F05.126, PO Box 85500, 3508 GA Utrecht, the Netherlands. Telephone number +31 88 75 530 68. Email [i.g.t.baeten@umcutrecht.nl](mailto:i.g.t.baeten@umcutrecht.nl).

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## 27 Abstract

### 28 Introduction

29 Nowadays, two predominant methods for detecting sentinel lymph nodes (SLNs) in cervical cancer are  
30 in use. The most conventional method is a combination of a radiotracer, technetium-99m ( $^{99m}\text{Tc}$ ), and  
31 blue dye. More recently another method for SLN mapping has emerged using indocyanine green (ICG).  
32 ICG is a fluorescent dye, visualised intraoperatively with near-infrared (NIR) fluorescence imaging,  
33 providing real-time visual navigation. The presumed advantages of ICG, i.e. cheaper, nonradioactive and  
34 logistically more attractive, are only valuable if its detection rate proves to be at least non-inferior to  
35  $^{99m}\text{Tc}$  and blue dye. Before omitting the well-functioning and evidence based combined approach of  
36  $^{99m}\text{Tc}$  and blue dye, we aim to provide prospective evidence on the non-inferiority of ICG with NIR  
37 fluorescence imaging.

### 38 Methods and analysis

39 We initiated a prospective, multicentre, non-inferiority study with a paired comparison of both SLN  
40 methods in a single sample of patients with FIGO stage IA–IB2 or IIA1 cervical cancer receiving primary  
41 surgical treatment. All patients undergo SLN mapping with ICG and NIR fluorescence imaging in adjunct  
42 to mapping with  $^{99m}\text{Tc}$  (including SPECT/CT) and blue dye. Surgeons start SLN detection with ICG while  
43 being blinded for the preoperative outcome of SPECT/CT to avoid biased detection with ICG. Primary  
44 endpoint of this study is bilateral SLN detection rate of both methods (i.e. detection of at least one SLN  
45 in each hemipelvis). Since we compare strategies for SLN mapping that are already applied in current  
46 daily practice for different types of cancer, no additional risks or burdens are expected from these study  
47 procedures.

### 48 Ethics and dissemination

49 The current study is approved by the Medical Ethics Research Committee (MREC) Utrecht (reference  
50 number 21-014). Findings arising from this study will be disseminated in peer-reviewed journals,  
51 academic conferences and through patient organisations.

52 **Trial registration number:** Netherlands Trial Register NL9011; EudraCT 2020-005134-15.

## Article Summary

### Strengths and limitations of this study

- We are the first to provide a powered, prospective comparison of bilateral sentinel node detection with ICG versus the combination of radiotracer (including preoperative imaging) and blue dye in cervical cancer.
- Given that the use of ICG has substantial benefits over the combined approach (no radiation, lower allergy risk and lower healthcare costs), a non-inferiority design is justified.
- The presented design allows for an intrapatient endpoint comparison which increases statistical power and – contrary to a randomised controlled trial – allows for a direct comparison of detection rate and sentinel lymph node anatomical localisation of the different tracers.
- Surgeons are blinded for the outcome of the radiotracer when starting sentinel lymph node detection with ICG.
- The lack of blinding for the outcome of blue dye, visible with the naked eye, is a limitation of this study design.

## Introduction

Lymph node status is the strongest prognostic factor of survival in cervical cancer patients and influences therapeutic management(1), highlighting the importance of nodal assessment. To assess nodal stage accurately and efficiently in early-stage cervical cancer patients, sentinel lymph node (SLN) mapping has emerged and could play a fundamental role in reducing the need for full pelvic lymphadenectomy. International studies are underway to assess the performance of SLN resection alone versus pelvic lymphadenectomy in cervical cancer treatment.(2, 3) For SLN mapping to be considered reliable, adequate detection and resection is essential. Since the cervix is a midline organ and lymphatic drainage is conducted bilaterally, high bilateral detection rates (defined as the proportion of patients with at least one SLN detected in each hemipelvis) are crucial for reliable SLN mapping.(4)

For mapping the SLNs, the conventional combined approach of radiotracer technetium-99m nanocolloid ( $^{99m}\text{Tc}$ ) and blue dye previously has proven to yield superior bilateral detection rates compared to using one of these tracers alone.(4-9) The radiotracer  $^{99m}\text{Tc}$  enables preoperative imaging with SPECT/CT while blue dye is added during surgery to visualize lymph nodes and afferent lymphatic vessels. However, certain disadvantages exist. Use of  $^{99m}\text{Tc}$  with SPECT/CT exposes patients to ionizing radiation. Intraoperatively, use of  $^{99m}\text{Tc}$  only gives acoustic feedback and, with conventional gamma probes, is unable to provide real-time visual guidance. The 'long' radiotracer protocol (i.e. one day preoperative admission for SPECT/CT) can be logistically challenging (demanding a nuclear medicine unit with safety protocols for handling), time consuming, involving longer hospital stay, and leading to higher patient

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3 92 burden. Also,  $^{99m}\text{Tc}$  usage is costly, especially in combination with preoperative SPECT/CT. Although the  
4 combination with intraoperative use of blue dye is beneficial in terms of bilateral detection rate, in a  
5 subset of patients blue dye is associated with allergic reactions, that may be severe (around 0.6%).(9, 10)  
6  
7 95 Common adverse effects related to blue dye are localized swelling or pruritus (2-4%), transient  
8 96 discolouration of skin and urine (>95%) and a decrease in pulse oximetry readings due to colorimetric  
9 97 interference.(11, 12)

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12 98 The aforementioned disadvantages contributed to the recent shift towards SLN mapping with  
13 99 indocyanine green (ICG).(13) ICG is a nonradioactive fluorescent dye that is visualised intraoperatively  
14 100 with near-infrared (NIR) fluorescence imaging, providing real-time visual navigation. Recently, the FDA  
15 101 approved ICG for the indication of lymphatic mapping in uterine and cervical cancers.(14) Compared to  
16 102  $^{99m}\text{Tc}$ , ICG is non-radioactive, cheaper and logically more attractive. Compared to blue dye, ICG has a  
17 103 better tissue penetration and a lower allergy risk. Overall, the use of ICG may lead to less burden on the  
18 104 patient as its use enables shorter hospital admissions and injection under anaesthesia. (15-17) The  
19 105 feasibility of ICG has been demonstrated and early reports showed ICG yields high SLN detection rates  
20 106 in patients with early-stage cervical cancer.(18-21) Limitations of ICG include costs of NIR fluorescence  
21 107 equipment and less guidance towards unexpected SLN positions because of the absence of preoperative  
22 108 imaging. (22) Another pitfall is the tissue penetration of NIR fluorescence imaging of approximately 1  
23 109 cm, meaning it can be detected through a centimetre of overlying tissue,(23) which is especially limiting  
24 110 in patients with a high body mass index.(24, 25) Also, the small hydrodynamic diameter of the ICG  
25 111 molecule may result in rapid spreading towards second and third echelon nodes,(16) undesirably leading  
26 112 to higher number of removed (false) SLNs. Although clinically the shift towards ICG seems to be in  
27 113 progress, shifting to an easy-to-use technique is not justified without prior evidence of its clinical  
28 114 reliability and validity wherein it performs at least as good as the current standard of care.

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30  
31 115 In both endometrial and cervical cancer prospective trials comparing ICG with the more conventional  
32 116 method of  $^{99m}\text{Tc}$  and blue dye are lacking.(26-29) The surgical practice has changed rapidly towards ICG  
33 117 in absence of level A evidence on its diagnostic accuracy. The unexpected recent findings of the LACC  
34 118 trial have again stressed the importance of compelling evidence before switching to a new surgical  
35 119 technique.(30) Regarding cervical cancer, a prospective study by Lührs et al. compared ICG with  
36 120 intraoperatively administered  $^{99m}\text{Tc}$  in 65 cervical cancer patients, without adding blue dye and without  
37 121 performing preoperative SPECT/CT imaging. The researchers reported a significant higher bilateral  
38 122 detection rate of ICG compared to  $^{99m}\text{Tc}$  without any significant improvement by combining the two.  
39 123 The lack of preoperative imaging in this study possibly affected the bilateral detection rate of  $^{99m}\text{Tc}$   
40 124 negatively, which was low at 60%.(31) The FILM trial, a randomised non-inferiority trial comparing ICG  
41 125 with blue dye for SLN mapping in predominantly endometrial cancer (n=169; 96%) though also cervical

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3 126 cancer (n=7; 4%), reported significantly higher SLN detection rates with ICG than with blue dye only.(29)  
4 127 Besides its limited applicability in cervical cancer, a second major limitation is the absence of a  
5 128 radiotracer, making a comparison between ICG and the conventional combined approach impossible.  
6  
7 129 Retrospective cohort studies reporting on the comparison of ICG versus  $^{99m}\text{Tc}$  combined with blue dye  
8 130 exist, but are generally of insufficient quality, underpowered and potentially suffer from publication bias.  
9 131 After a systematic review and meta-analysis of the available literature comparing ICG with  $^{99m}\text{Tc}$  and blue  
10 132 dye, we found that the pooled bilateral detection rate with ICG appeared to be significantly higher.(32)  
11 133 However, in adherence with the Grading of Recommendations, Assessment, Development, and  
12 134 Evaluation (GRADE) guidelines, the quality of evidence was too low to provide strong recommendations  
13 135 and directly omit the combined approach of a radiotracer and blue dye. In addition, all included studies  
14 136 reported a higher average number of identified SLNs when using ICG as a tracer, indicating these are  
15 137 not likely to be all SLNs but rather second echelon lymph nodes. Failing to excise the true SLN could  
16 138 result in missed lymph node metastases.

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18 139 Before omitting any well-functioning and evidence based procedure ( $^{99m}\text{Tc}$  combined with blue dye)  
19 140 high quality evidence on the performance of ICG in cervical cancer SLN mapping is needed. In the FILM  
20 141 trial by Frumovitz et al. it was stated: "*Although the combination of blue dye and radiocolloid might be*  
21 142 *better than blue dye alone and equivalent to indocyanine green in detecting sentinel nodes, no studies –*  
22 143 *either prospective or retrospective – have compared the combination of blue dye and radiocolloid with*  
23 144 *indocyanine green.*".(29) With our study, we intend to perform the proposed prospective study  
24 145 comparing ICG with the combination of radiotracer and blue dye (including preoperative SPECT/CT) in  
25 146 early-stage cervical cancer patients. The presumed benefits of ICG are only valuable if its detection rate  
26 147 proves to be at least non-inferior to  $^{99m}\text{Tc}$  and blue dye.

## 42 148 Methods and analysis

### 43 149

### 44 150 Study design

45 151 The FluoreSENT study is initially designed as a prospective, multicentre, non-randomised, single-arm,  
46 152 cross-sectional study in which we compare two SLN methods in early-stage cervical cancer patients  
47 153 undergoing primary surgical treatment (FIGO stage IA – IB2 or IIA1): ICG with NIR fluorescence imaging  
48 154 versus  $^{99m}\text{Tc}$  (including preoperative SPECT/CT) and blue dye. The study is coordinated by the University  
49 155 Medical Center Utrecht (UMCU) and monocentric in the rollout phase (start date July 2021). We plan to  
50 156 expand this study in other Dutch tertiary referral centres to increase the accrual rate.  
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3 158 Given that the current bilateral detection rate using  $^{99m}\text{Tc}$  combined with blue dye is already high (86%  
4 in own cohort) and the use of ICG has substantial benefits, a non-inferiority design is justified.(33) When  
5 non-inferiority is reached, a switch in standard care to ICG with NIR fluorescence imaging (i.e.  
6 abandoning  $^{99m}\text{Tc}$  and blue dye) is supported. It is important to note that this is not an equivalence trial.  
7  
8 161 When SLN mapping with ICG produces a higher bilateral detection rate than SLN mapping with  $^{99m}\text{Tc}$   
9 and blue dye, this is not considered a negative study result, whereas this is clearly a convincing reason  
10 to change the current practice. We chose bilateral detection rate as the primary endpoint because  
11 bilateral detection of SLNs has proven to decrease false negative rate and is thus considered to improve  
12 reliability and oncological safety.(4, 34) This protocol has been developed in line with research protocol  
13 template of the Central Committee on Research Involving Human Subjects (CCMO) and the SPIRIT  
14 recommendations.(35)  
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18 170 **Study population**  
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20 171 The subjects will be drawn from a population of patients with histopathologically proven primary  
21 malignancy of the cervix uteri. Patients are eligible to participate if they are planned for a (robot-assisted)  
22 laparoscopic or open SLN procedure as part of the standard surgical treatment for FIGO stage IA1-IB2  
23 or II A cervical cancer (according to the FIGO 2018 guidelines(36)), aged  $\geq 18$  years and able to provide  
24 informed consent. Exclusion criteria are: pregnancy or current breastfeeding, renal insufficiency stage 3  
25 or 4, prior allergic reaction to ICG,  $^{99m}\text{Tc}$  or patent blue, prior severe allergic reaction to iodine. Informed  
26 consent will be obtained before the start of any study activity.  
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30 179 **Sample size**  
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32 180 The sample size calculation was based on our own data and current literature. Data from our historical  
33 cohort showed a bilateral detection proportion of 86% (95% CI 80-91%) for SLN mapping with  $^{99m}\text{Tc}$  and  
34 blue dye (manuscript in preparation; (33)). The pooled proportion of bilateral detection rate of ICG was  
35 found to be between 89.4% and 91.5%, depending on how studies in the meta-analysis were handled  
36 (in preliminary analysis). Based on consensus discussion by clinicians in the study team and a  
37 comprehensive review of the literature, a non-inferiority margin of 0.05 was set. For assessing non-  
38 inferiority in paired proportions the asymptotic test statistic, which is the so-called Nam score test,  
39 or restricted maximum likelihood estimation (RMLE-based) test statistic was used.(37) The power and  
40 sample size was calculated in the statistical software package PASS (Power Analysis and Sample Size),  
41 verified for non-inferiority tests (one-sided) for two correlated proportions.(38) The calculations were  
42 checked by a statistician (power formula is provided in the PASS User's Guide(38)).  
43  
44 191 In conclusion, comparing a proportion ( $^{99m}\text{Tc}$  and blue dye at 0.86, ICG 0.89) in one sample with a non-  
45 inferiority margin of 0.05, with a Type I error ( $\alpha$ ) set at 0.05, Type II error ( $\beta$ ) set at 0.2 (power  $1-\beta = 0.8$ ),  
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3 193 and Nuisance set at 0.12 (based on the proportion of discordant pairs), we require a sample size of 101  
4 cases. The complete list of parameters used for the power calculation is provided in the Supplementary  
5 File.  
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9 196 **Investigational product**  
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11 197 ICG is a fluorescent agent used for diagnostic purposes in adults and children with a benign safety  
12 profile. One of the diagnostic purposes is fluorescence imaging of lymph nodes and delineation of  
13 lymphatic vessels in the cervix and uterus in patients with solid tumours during lymphatic mapping. No  
14 therapeutic effects are expected. ICG (VERDYE 25mg, Diagnostic Green GmbH, Germany) is registered  
15 for diagnostic purposes in adults under Dutch RVG number 31052.  
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18 201 Allergic reactions and anaphylactic shocks due to ICG were reported in very rare (<0.01%) cases. In  
19 patients with renal insufficiency, the risk of anaphylactic shock appears to be higher. In very rare cases  
20 spasms of the coronary arteries are described. Radioactive iodine uptake studies should not be  
21 performed for at least a week following the use of ICG. No other complications or potential risks of ICG  
22 are reported.(14)  
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26 207 **Trial intervention**  
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28 208 The flowchart in **Figure 1** presents a schematic overview of the study design. All subjects undergo a SLN  
29 procedure as part of the surgical treatment and receive ICG injection in adjunct to the current combined  
30 approach. Subjects will be preoperatively injected with  $^{99m}\text{Tc}$  followed by a SPECT/CT 90-120 minutes  
31 post-injection (according to current standard-of-care).(33) The surgeon (gynaecological oncologist) will  
32 not consult the SPECT/CT preoperatively (secured by automated logging of consultation). At the start of  
33 surgery, subjects are injected with four millilitres of ICG 1.25 mg/ml (study procedure) and four millilitres  
34 of blue dye (standard-of-care) under general anaesthesia; 1 ml of both tracers into each quadrant of the  
35 cervix. During surgery the SLNs will be first identified with NIR fluorescence light using FireFly fluorescent  
36 imaging system (Intuitive Surgical Inc.) in robotic surgery or a CE marked NIR fluorescence platform  
37 applicable to laparoscopic or laparotomic surgery; in this light NIR fluorescent nodes will light up green  
38 (**Figure 2**). Localisation of each NIR fluorescent SLN will be reported. When the NIR fluorescent SLN(s)  
39 are identified, the gynaecological oncologist will check the SLN(s) for radioactivity with a gamma probe  
40 (either *in vivo* or *ex vivo*) and blue colour. When completed, the procedure is repeated in the  
41 contralateral hemipelvis. Results are reported as follows: of each SLN the localisation is reported  
42 according to a standardised format (appendix) and it is stated if detected with NIR fluorescence (ICG),  
43 radioactivity ( $^{99m}\text{Tc}$ ) and/or blue colour (blue dye). All SLNs identified are excised. After finishing this  
44 procedure bilaterally, the surgeon consults the SPECT/CT (time of deblinding is logged both  
45 automatically and manually) and reports whether radioactive node(s) on SPECT/CT correspond to the  
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3 226 excised SLN(s). To prevent missing SLNs, the pelvic site will be checked for residual radioactive nodes  
4 and blue nodes, and excised, if present. Residual radioactivity of the surgical site will be measured and  
5 deemed negative if background counts are less than 10% of the maximum SLN count.  
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9 229 Blue dye and ICG are injected sequentially, before entering the retroperitoneal space. Previous studies  
10 using a combined injection of patent blue and ICG experienced no clotting of the two dyes, both at  
11 macroscopic and microscopic level.(39-41) To prevent from bias in detection of SLNs, injecting blue dye  
12 in a later stage of surgery – i.e. after SLN mapping with ICG and NIR fluorescence is completed – has  
13 been explored. However, starting SLN mapping with ICG would result in anatomical structures and  
14 lymphatic vessels that have already been destructed. Because of the destructed lymph vessels, injecting  
15 blue dye in a later stage would underestimate the true benefit as the dye will not reach the lymph nodes.  
16  
17 233 This intrapatient study design is thereby limited by the inability of blinding for the outcome of blue dye.  
18  
19 236 Except for injection of ICG and detection with NIR fluorescence imaging while blinded for the assessment  
20 of the SPECT/CT, the complete treatment is maintained according to the current standard-of-care.  
21  
22 239 Intraoperative recordings and pictures can be made for retrospective tumour-to-background ratio  
23 analysis. All follow-up visits take place according to the national guidelines. There is no special follow-  
24 up required for subjects in this study. Subjects are asked to fill in the IN-PATSAT32 questionnaire  
25 postoperatively, developed by European Organisation for Research and Treatment of Cancer (EORTC),  
26 for assessing patients' perception of the quality of hospital-based care (not mandatory).  
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30 244 **Outcomes**  
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34 245 The primary outcome is bilateral detection rate of SLNs with ICG and NIR fluorescence imaging versus  
35  $^{99m}\text{Tc}$  (including pre-operative SPECT/CT) and blue dye. SLN is defined as the first lymph node(s) of each  
36 hemipelvis to receive afferent lymphatic drainage from the primary cervical tumour, identified by either  
37 ICG, gamma radiation using  $^{99m}\text{Tc}$  or blue dye. Bilateral detection is defined as number of patients  
38 detected with at least one SLN in each hemipelvis.  
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42 250 Secondary outcomes include: (1) overall (i.e. at least unilateral) detection rate, sensitivity and false  
43 negative rate (FNR) of ICG and  $^{99m}\text{Tc}$  and blue dye, with pelvic lymph node dissection (PLND) as the  
44 reference standard to confirm tumour positive lymph nodes (part of current standard-of-care); (2)  
45 correlation between NIR fluorescent, radioactive (both intraoperative and with SPECT/CT) and blue  
46 stained SLNs in terms of anatomical location; (3) adverse events of ICG,  $^{99m}\text{Tc}$  and blue dye; (4) time to  
47 complete SLN detection with ICG versus  $^{99m}\text{Tc}$  and blue dye; (5) cost-effectiveness comparison (cost of  
48 procedure versus yielded bilateral detection rate) of ICG versus  $^{99m}\text{Tc}$  and blue dye SLN detection; (6)  
49 surgical evaluation of NIR fluorescent imaging (usability) measured with two short questionnaires  
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3 258 tailored for the surgeons; and (7) patient satisfaction with the oncological care and procedure measured  
4 259 with the validated EORTC IN-PATSAT32 questionnaire.  
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8 260 The basic clinical, surgical and histopathological parameters will be recorded, including: age at diagnosis,  
9 261 body mass index (BMI, in kg/m<sup>2</sup>), history of abdominal surgery, ASA classification (American Society of  
10 262 Anaesthesiologists), FIGO stage (2018), type of procedure, tumour histology and size, lymph vascular  
11 263 space invasion (LVSI), nodal count and status, parametrial involvement, vaginal involvement, positive  
12 264 resection margins, and adjuvant or adjusted treatment (the latter due to intraoperative finding of  
13 265 positive lymph nodes). Subanalysis will evaluate if these parameters are possible confounders or effect  
14 266 modifiers.  
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22 **268 Data collection and management**  
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24 269 All measurements will be systematically recorded using an electronic Clinical Report Form (eCRF) build  
25 in Castor Electronic Data Capture (EDC) system. Data will be collected in coded form and monitored by  
26 data managers from the UMC Utrecht. Baseline characteristics are collected pseudonymously from the  
27 medical records in consultation with the data management department of the research centre(s). All  
28 study procedures at the research centre(s) are monitored by an independent monitor during multiple  
29 visits according to a specified protocol.  
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31 274 The principal investigators at the research centre(s) bear responsibility for safe data handling. After the  
32 project is finished, data will be stored for 25 years according to the current Medical Research Involving  
33 Human Subjects Act (WMO). Handling of personal data will comply with the EU General Data Protection  
34 Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.  
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40 **279 Adverse events**  
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42 280 Adverse events are defined as any undesirable experience occurring to a subject during the study,  
43 whether or not considered related to the intervention (SLN mapping with ICG and NIR fluorescence). All  
44 281 adverse events reported spontaneously by the subject or observed by the investigator or his staff will be  
45 recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs in the  
46 283 48 hours following the SLN procedure. The sponsor will report the SAEs through the Dutch web portal  
47 284 ToetsingOnline to the accredited MREC that approved the protocol, within 7 days of first knowledge for  
48 285 SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete  
49 286 the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after  
50 287 the sponsor has first knowledge of the serious adverse events.  
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58 **289 Statistical analysis**  
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3 290 We will perform a comparison (single sample) of two diagnostic modalities and aim to assess non  
4 inferiority (note: not equivalence) of the ICG SLN mapping in terms of bilateral detection rate. Our  
5 analysis is based on previous literature on non-inferiority for paired binary data.(37) Statistical software  
6 programs SPSS and R will be used to perform the analyses. The measured primary endpoint is the  
7 proportion of bilateral SLN detection which is tested in a paired setting. The null(H0) and alternative(H1)  
8 hypotheses for this non-inferiority study are as follows:  
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- 14 296 • *H0*: SLN mapping with ICG is inferior to SLN mapping with  $^{99m}\text{Tc}$  and blue dye with respect to  
15 297 the proportion of bilaterally detected sentinel nodes.
- 16 298 • *H1*: SLN mapping with ICG is non-inferior to SLN mapping with  $^{99m}\text{Tc}$  and blue dye with respect  
17 299 to the proportion of bilaterally detected sentinel nodes.

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21  
22 301 The analysis of all outcome data will be performed using intrapatient comparison (McNemars test).  
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24 302 Categorical and continuous data will be presented in a quantitative way. The bilateral detection rates of  
25 303 ICG,  $^{99m}\text{Tc}$  and blue dye are presented separately with corresponding 95% confidence intervals.  
26  
27 304 Categorical data will be analysed using the Fisher Exact or Chi-square, as appropriate. For continuous  
28 305 outcomes t-test will be used in case of normally distributed data. If not normally distributed, Mann-  
29 306 Whitney-U test will be performed. Besides 95% confidence intervals, p-values will be reported with a  
30 307 value of <0.05 considered significant.  
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34 308 In case of identified inconsistencies or missing data, additional source documents will be requested from  
35 309 the study site to resolve ongoing inconsistencies. If necessary, patients are called to resolve missing data.  
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38 310 If missing data restrict further analysis, multiple imputation analyses will be conducted.  
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#### 40 311 **Patient and public involvement**

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42 312 Members of patient organisation Stichting Olijf were involved in the design of this study.  
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#### 45 313 **Ethics and dissemination**

46  
47 314 This current study was approved by Institutional Review Board and Medical Research Ethics Committee  
48  
49 315 Utrecht (number 21-014) in accordance with the Dutch Medical Research Involving Human Subjects Act  
50  
51 316 (WMO) and other applicable Dutch and European guidelines, regulations and Acts. The study was  
52  
53 registered in the Netherlands Trial Register (number NL9011). All subjects will have to sign and date  
54  
55 written informed consent. No study activities will occur prior to obtaining consent. Subjects retain the  
56  
57 right to withdraw at any point for any reason.  
58  
59 320 This study has been assessed as a low risk study. ICG is given in adjunct to the current standard of care  
60 and subjects are not withheld of any type of standard treatment. Risks associated with participation can

1  
2  
3 322 be considered negligible. Participating in this study will be associated with minor discomfort and might  
4 323 be beneficial for individuals, as mapping with ICG might result in higher SLN detection rates (based on  
5 324 previous literature). This study intends to improve oncological care and prognosis for all early-stage  
6 325 cervical cancer patients.  
7  
8

9  
10 326 We will ensure our findings and the acquired knowledge will be transferred to clinicians and researchers  
11 327 in the field. Findings arising from this study will be published at national and international conferences.  
12  
13 328 The final manuscript will be submitted for publication to an open access peer-reviewed scientific journal.  
14  
15 329 Both positive and negative trial results will be disclosed. Results will also be updated in the Netherlands  
16 330 Trial Register, which is the primary registry for the Netherlands and recognized and accepted by the  
17 WHO and ICMJE. Subjects and cervical cancer patients will be informed about the study results by the  
18 newsletter and social media accounts of patient organisation Stichting Olijf.  
19  
20 332  
21  
22 333

23 334 **Author contributions**

24  
25 335 IGT Baeten: Conceptualization, Methodology, Writing – Original Draft, Visualization.

26 336 JP Hoogendam: Conceptualization, Methodology, Writing - Original Draft, Validation (as  
27 epidemiologist and fellow gynaecological oncology).

28  
29 338 AJAT Braat: Methodology, Validation (as radiologist with expertise in nuclear medicine and use of  
30 339 technetium-99m SPECT/CT imaging), Writing - Review & Editing.

31  
32 340 WB Veldhuis: Validation (as radiologist with expertise in gynaecologic oncology), Writing - Review &  
33 341 Editing.

34  
35 342 GN Jonges: Validation (as pathologist with expertise in pathological assessment of SLNs and cervical  
36 343 cancer), Writing - Review & Editing.

37  
38 344 IM Jürgenliemk-Schulz: Validation (as radiation oncologist with expertise in cervical cancer treatment),  
39 345 Writing - Review & Editing.

40  
41 346 RP Zweemer: Conceptualization, Methodology, Validation (as gynaecological oncologist), Writing -  
42 347 Review & Editing.

43  
44 348 CG Gerestein: Conceptualization, Methodology, Validation (as gynaecological oncologist), Writing -  
45 349 Review & Editing, Supervision.

46  
47 350

48 351 **Funding statement**

49  
50 352 In the set-up and rollout phase this research received no specific grant from any funding agency in the  
51 353 public, commercial or not-for-profit sectors. We are awaiting the decision on the grant application to  
52 354 the Dutch Cancer Society (KWF), call 2022-I. If the application is granted, KWF is not going to be involved  
53 355 in collection, management, analysis and interpretation of data, writing of the manuscript and decision  
54 356 to submit the manuscript for publication, nor does it have authority over the publications.







**Figure legends**

**Figure 1.** Flowchart of study procedures. Blue boxes represent the current standard of care; red boxes represent the study specific procedures.

**Figure 2.** Fluorescence guided surgery showing lymphatic vessels (left) and sentinel lymph node (right).

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ICG = Indocyanine Green

NIR = Near-infrared

 $^{99m}\text{Tc}$  = Technetium-99m nanocolloid

Blue dye = patent blue

SLN(s) = Sentinel Lymph Node(s)

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13

September

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Surgeons blinded for assessment  
SPECT-CT

### One day preoperative BMJ Open

- Injection of  $^{99m}\text{Tc}$
- SPECT-CT 90 minutes post-injection

### Day of surgery

Start of (robot-assisted) laparoscopy or laparotomy

Injection of **blue dye** into 4 quadrants

Injection of **ICG** into 4 quadrants

*Start surgery*

Identification of **NIR fluorescent** (ICG positive) SLNs

*Using the NIR fluorescence camera*

*Consultation of SPECT-CT*

Identification of any residual radioactive ( $^{99m}\text{Tc}$  positive) SLNs

*Using the gamma probe*

Identification of any residual **blue** SLNs

*Sent all SLNs for frozen section analysis*

Identification of **NIR fluorescent** SLN(s)
 

- Report localisation of SLN(s)
- Evaluation of radioactivity and blue dye *in vivo*
- Excision of SLN(s)

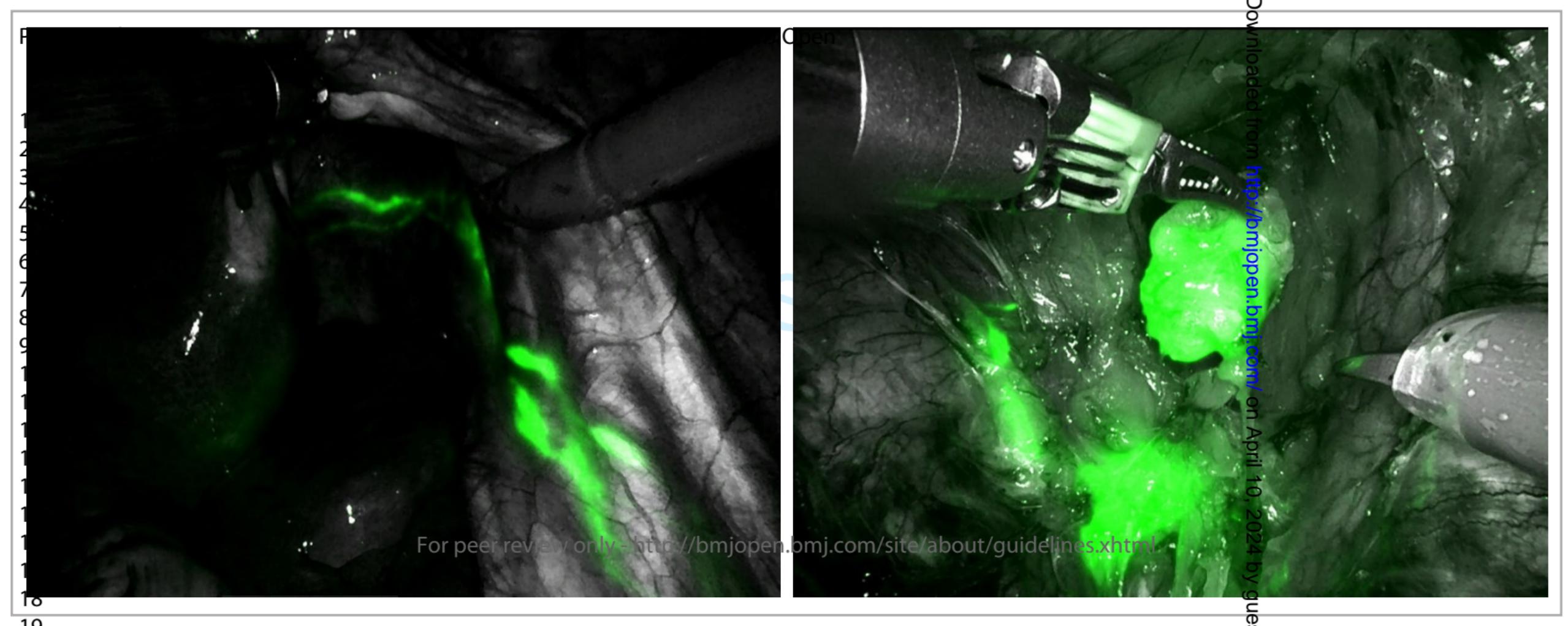
Identification of residual **radioactive** SLN(s)
 

- Report localisation of residual SLN(s)
- Evaluation of NIR fluorescence and blue dye *in vivo*
- Excision of SLN(s)

Identification of residual **blue** SLN(s)
 

- Report localisation of residual SLN(s)
- Evaluation of NIR fluorescence and radioactivity *in vivo*
- Excision of SLN(s)

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Pelvic lymph node dissection



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### Supplementary file

#### **Sample size calculation**

For assessing non-inferiority in paired proportions we will use an asymptotic test statistic, which is the so-called Nam score test, or restricted maximum likelihood estimation (RMLE-based) test statistic.<sup>(1)</sup> The power and sample size was calculated in the statistical software package PASS (Power Analysis and Sample Size), verified for non-inferiority tests (one-sided) for two correlated proportions.<sup>(2)</sup> The calculations were checked by a statistician (the power formula is given in the PASS User's Guide).

We set the following parameters in PASS based on consensus discussion by the clinicians in our study team and a comprehensive review of the aforementioned literature:

- *Power* is the probability of rejecting a false null hypothesis. Set at 0.80.
- *Equivalence Difference (De)* is the maximum difference between the two proportions that is still called 'equivalent.' Set at 0.05 (equal to the non-inferiority margin).
- *Actual Difference (Da)* is the actual difference between Pt and Ps. That is, Da = Pt-Ps. Set at 0.03.
- *Treatment Proportion (Pt)* is the response proportion to the treatment (experimental or new) test. Set at 0.89.
- *Standard Proportion (Ps)* is the response proportion to the standard (reference or old) test. Set at 0.86.
- The *Nuisance Parameter* is a value that is needed, but is not a direct part of the hypothesis. The parameter is based on the proportion of discordant pairs. Set at 0.12.
- *Alpha ( $\alpha$ )* is the probability of rejecting a true null hypothesis. Set at 0.05.
- *Beta ( $\beta$ )* is the probability of accepting a false null hypothesis. Set at 0.20

#### **References**

1. Liu JP, Hsueh HM, Hsieh E, Chen JJ. Tests for equivalence or non-inferiority for paired binary data. *Stat Med*. 2002 Jan 30;21(2):231-45.
2. Hintze JL. Non-Inferiority Tests for Two Correlated Proportions. *PASS User's Guide I*. Kaysville, Utah: NCSS; 2008. p. 221-36.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <b>Manuscript page 1</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <b>Netherlands Trial Registry: number NL9011 (see Page 2).</b>
	2b	All items from the World Health Organization Trial Registration Data Set <b>For the Netherlands the NTR is the Primary Registry accepted by the WHO and ICMJE.</b>
Protocol version	3	Date and version identifier <b>01-07-2021 / NL75722.041.20 / version 1.4</b>
Funding	4	Sources and types of financial, material, and other support <b>Funding, manuscript page 11</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <b>Check (described on title page of study protocol)</b>
	5b	Name and contact information for the trial sponsor <b>Check; UMC Utrecht (described in study protocol)</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <b>Check (described in study protocol)</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <b>Check (described in study protocol)</b>

**Introduction**

		Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <b>Introduction, manuscript page 3 - 5</b>
		Objectives	6b	Explanation for choice of comparators <b>Introduction, manuscript page 3 – 5</b>
		Trial design	7	Specific objectives or hypotheses <b>Introduction, page 3 – 5, and Statistical analysis, manuscript page 10</b>
			8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <b>Methods, Study design, manuscript page 5</b>

## Methods: Participants, interventions, and outcomes

		Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <b>Methods, Study population, manuscript page 5</b>
		Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <b>Methods, Study design and Study population, manuscript page 5-6</b>
		Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <b>Methods, manuscript page 7</b>
			11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <b>Not applicable</b>
			11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <b>Not applicable</b>
			11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <b>Methods, Trial intervention, manuscript page 7</b>

1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <a href="#">Methods, Outcomes, manuscript page 8</a>
11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <a href="#">See flow chart in Figure 1 of the manuscript</a>
17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <a href="#">Methods, Sample size, manuscript page 6</a>
22	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <a href="#">Check (recruitment and informed consent procedure are described in study protocol)</a>

### 28           **Methods: Assignment of interventions (for controlled trials)**

#### 30           Allocation:

32	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions <a href="#">Not applicable</a>
41	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned <a href="#">Not applicable</a>
49	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions <a href="#">Not applicable</a>
53	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Not applicable</a>

- 1  
2      17b If blinded, circumstances under which unblinding is permissible, and  
3                    procedure for revealing a participant's allocated intervention during  
4                    the trial  
5                    Not applicable  
6

7      **Methods: Data collection, management, and analysis**  
8

- 9  
10     Data collection methods      18a Plans for assessment and collection of outcome, baseline, and other  
11                    trial data, including any related processes to promote data quality (eg,  
12                    duplicate measurements, training of assessors) and a description of  
13                    study instruments (eg, questionnaires, laboratory tests) along with  
14                    their reliability and validity, if known. Reference to where data  
15                    collection forms can be found, if not in the protocol  
16                    **Methods, Data collection and management, manuscript page 9**  
17  
18     Data management      18b Plans to promote participant retention and complete follow-up,  
19                    including list of any outcome data to be collected for participants who  
20                    discontinue or deviate from intervention protocols  
21                    Not applicable  
22  
23     Statistical methods      19      Plans for data entry, coding, security, and storage, including any  
24                    related processes to promote data quality (eg, double data entry;  
25                    range checks for data values). Reference to where details of data  
26                    management procedures can be found, if not in the protocol  
27                    **Methods, Data collection and management, manuscript page 9. Also,**  
28                    **there is a reference to Datamanagement plan in study protocol.**  
29  
30  
31  
32  
33     Statistical methods      20a Statistical methods for analysing primary and secondary outcomes.  
34                    Reference to where other details of the statistical analysis plan can be  
35                    found, if not in the protocol  
36                    **Methods, Statistical analysis, manuscript page 10**  
37  
38     Statistical methods      20b Methods for any additional analyses (eg, subgroup and adjusted  
39                    analyses)  
40                    **Methods, Statistical analysis, manuscript page 10**  
41  
42     Statistical methods      20c Definition of analysis population relating to protocol non-adherence  
43                    (eg, as randomised analysis), and any statistical methods to handle  
44                    missing data (eg, multiple imputation)  
45                    **Check (handling missing data is described in study protocol).**  
46  
47  
48  
49      **Methods: Monitoring**  
50  
51     Data monitoring      21a Composition of data monitoring committee (DMC); summary of its role  
52                    and reporting structure; statement of whether it is independent from  
53                    the sponsor and competing interests; and reference to where further  
54                    details about its charter can be found, if not in the protocol.  
55                    Alternatively, an explanation of why a DMC is not needed  
56                    **Methods, Data collection and management, manuscript page 9.**  
57                    **Independent monitor has been assigned.**  
58  
59  
60

1	21b	Description of any interim analyses and stopping guidelines, including 3 who will have access to these interim results and make the final 4 decision to terminate the trial  <b>Not applicable</b>
5	Harms	22 Plans for collecting, assessing, reporting, and managing solicited and 6 spontaneously reported adverse events and other unintended effects 7 of trial interventions or trial conduct  <b>Check (described in study protocol according to the CCMO 8 guidelines)</b>
9	Auditing	23 Frequency and procedures for auditing trial conduct, if any, and 10 whether the process will be independent from investigators and the 11 sponsor  <b>Check (reference to written monitor plan in protocol)</b>
<b>Ethics and dissemination</b>		
12	Research ethics approval	24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval  <b>Approval has been obtained.</b>
13	Protocol amendments	25 Plans for communicating important protocol modifications (eg, 14 changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, 15 regulators)  <b>Check (described in study protocol according to the CCMO 16 guidelines)</b>
17	Consent or assent	26a Who will obtain informed consent or assent from potential trial 18 participants or authorised surrogates, and how (see Item 32)  <b>Check (recruitment and informed consent procedure are described 19 in study protocol)</b>
20		26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable  <b>Not applicable</b>
21	Confidentiality	27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  <b>Check (reference to written Datamanagement plan in study protocol)</b>
22	Declaration of interests	28 Financial and other competing interests for principal investigators for the overall trial and each study site  <b>Competing interests, manuscript page 12</b>
23	Access to data	29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators  <b>Check (reference to written Datamanagement plan in study protocol)</b>

- 1 Ancillary and  
2 post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for  
3 compensation to those who suffer harm from trial participation  
4 **Check (liability insurance and participant insurance are taken out by  
5 the study sponsor)**
- 6 Dissemination  
7 policy 31a Plans for investigators and sponsor to communicate trial results to  
8 participants, healthcare professionals, the public, and other relevant  
9 groups (eg, via publication, reporting in results databases, or other  
10 data sharing arrangements), including any publication restrictions  
11 **Check (written Dissemination plan)**
- 12 31b Authorship eligibility guidelines and any intended use of professional  
13 writers  
14 **Check**
- 15 31c Plans, if any, for granting public access to the full protocol, participant-  
16 level dataset, and statistical code  
17 **Check (reference to written Datamanagement plan in study protocol)**

## 23 Appendices

- 24 Informed consent 32 Model consent form and other related documentation given to  
25 materials participants and authorised surrogates  
26 **Check (reference to written patient information in study protocol)**
- 27 Biological 33 Plans for collection, laboratory evaluation, and storage of biological  
28 specimens specimens for genetic or molecular analysis in the current trial and for  
29 future use in ancillary studies, if applicable  
30 **Not applicable**

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

# BMJ Open

## **Fluorescent indocyanine green versus technetium-99m and blue dye for bilateral SENTinel lymph node detection in stage I-IIA cervical cancer (FluoreSENT): protocol for a non-inferiority study**

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Complete List of Authors:	Baeten, Ilse; UMC Utrecht, Department of Gynaecologic Oncology Hoogendam, Jacob; UMC Utrecht, Department of Gynaecologic Oncology Braat, Arthur; UMC Utrecht, Department of Radiology and Nuclear Medicine Veldhuis, Wouter; UMC Utrecht, Department of Radiology and Nuclear Medicine Jonges, Geertruida; UMC Utrecht, Department of Pathology, Division of Laboratory, Pharmacy and Biomedical Genetics Jürgenliemk-Schulz, Ina; UMC Utrecht, Department of Radiotherapy Zweemer, Ronald; UMC Utrecht, Department of Gynaecologic Oncology Gerestein, Cornelis; UMC Utrecht, Department of Gynaecologic Oncology
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	ONCOLOGY, Nuclear radiology < RADIOLOGY & IMAGING, Diagnostic radiology < RADIOLOGY & IMAGING, Gynaecological oncology < ONCOLOGY, GYNAECOLOGY

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Manuscripts

**Protocol manuscript BMJ Open REVISED - v1.1 - bmjopen-2022-061829.R1****Title**

Fluorescent indocyanine green versus technetium-99m and blue dye for bilateral SENTinel lymph node detection in stage I-IIA cervical cancer (FluoreSENT): protocol for a non-inferiority study

**Authors:**

Ilse G.T. Baeten<sup>a</sup> MD, Jacob P. Hoogendam<sup>a</sup> MD PhD, Arthur J.A.T. Braat<sup>b</sup> MD PhD, Wouter B. Veldhuis<sup>b</sup> MD PhD, Geertruida N. Jonges<sup>c</sup> MD PhD, Ina M. Jürgenliemk-Schulz<sup>d</sup> MD PhD, Ronald P. Zweemer<sup>a</sup> MD PhD, Cornelis G. Gerestein<sup>a</sup> MD PhD

<sup>a</sup> Department of Gynaecologic Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>b</sup> Department of Radiology and Nuclear Medicine, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>c</sup> Department of Pathology, Division of Laboratory, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>d</sup> Department of Radiotherapy, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

**Corresponding author:** Ilse G.T. Baeten MD, Department of Gynaecological Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, F05.126, PO Box 85500, 3508 GA Utrecht, the Netherlands. Telephone number +31 88 75 530 68. Email [i.g.t.baeten@umcutrecht.nl](mailto:i.g.t.baeten@umcutrecht.nl).

**Word count (excluding abstract and references):** 3905

## 27 Abstract

### 28 Introduction

29 Nowadays, two predominant methods for detecting sentinel lymph nodes (SLNs) in cervical cancer are  
30 in use. The most conventional method is a combination of a radiotracer, technetium-99m ( $^{99m}\text{Tc}$ ), and  
31 blue dye. More recently another method for SLN mapping using indocyanine green (ICG) is becoming  
32 widely accepted. ICG is a fluorescent dye, visualised intraoperatively with near-infrared (NIR)  
33 fluorescence imaging, providing real-time visual navigation. The presumed advantages of ICG over  $^{99m}\text{Tc}$ ,  
34 i.e. cheaper, nonradioactive and logically more attractive, are only valuable if its detection rate proves  
35 to be at least non-inferior. Before omitting the well-functioning and evidence based combined approach  
36 of  $^{99m}\text{Tc}$  and blue dye, we aim to provide prospective evidence on the non-inferiority of ICG with NIR  
37 fluorescence imaging.

### 38 Methods and analysis

39 We initiated a prospective non-inferiority study with a paired comparison of both SLN methods in a  
40 single sample of 101 patients with FIGO stage IA–IB2 or IIA1 cervical cancer receiving primary surgical  
41 treatment. All patients undergo SLN mapping with ICG and NIR fluorescence imaging in adjunct to  
42 mapping with  $^{99m}\text{Tc}$  (including SPECT/CT) and blue dye. Surgeons start SLN detection with ICG while  
43 being blinded for the preoperative outcome of SPECT/CT to avoid biased detection with ICG. Primary  
44 endpoint of this study is bilateral SLN detection rate of both methods (i.e. detection of at least one SLN  
45 in each hemipelvis). Since we compare strategies for SLN mapping that are already applied in current  
46 daily practice for different types of cancer, no additional risks or burdens are expected from these study  
47 procedures.

### 48 Ethics and dissemination

49 The current study is approved by the Medical Ethics Research Committee (MREC) Utrecht (reference  
50 number 21-014). Findings arising from this study will be disseminated in peer-reviewed journals,  
51 academic conferences and through patient organisations.

52 **Trial registration number:** Netherlands Trial Register NL9011; EudraCT 2020-005134-15.

## Article Summary

### Strengths and limitations of this study

- We perform a powered, prospective non-inferiority trial comparing the bilateral sentinel node detection with ICG versus the combination of radiotracer (including preoperative imaging) and blue dye in cervical cancer.
- The FluoreSENT study is designed for intrapatient endpoint comparison, which increases statistical power and – contrary to a randomised controlled trial – allows for a direct comparison of detection rate and sentinel lymph node anatomical localisation of the different tracers.
- In the presented design, surgeons are blinded for the outcome of the radiotracer when starting sentinel lymph node detection with ICG.
- A limitation of this study design is the lack of blinding for the outcome of blue dye, which is visible with the naked eye.

### Introduction

Lymph node status is the strongest prognostic factor of survival in cervical cancer patients and influences therapeutic management(1), highlighting the importance of nodal assessment. To assess nodal stage accurately and efficiently in early-stage cervical cancer patients, sentinel lymph node (SLN) mapping has emerged and could play a fundamental role in reducing the need for full pelvic lymphadenectomy. International studies are underway to assess the performance of SLN resection alone versus pelvic lymphadenectomy in cervical cancer treatment.(2, 3) For SLN mapping to be considered reliable, adequate detection and resection is essential. Since the cervix is a midline organ and lymphatic drainage is conducted bilaterally, high bilateral detection rates (defined as the proportion of patients with at least one SLN detected in each hemipelvis) are crucial for reliable SLN mapping.(4)

For mapping the SLNs, the conventional combined approach of radiotracer technetium-99m nanocolloid ( $^{99m}\text{Tc}$ ) and blue dye previously has proven to yield superior bilateral detection rates compared to using one of these tracers alone.(4-9) The radiotracer  $^{99m}\text{Tc}$  enables preoperative imaging with SPECT/CT while blue dye is added during surgery to visualize lymph nodes and afferent lymphatic vessels. However, certain disadvantages exist. Use of  $^{99m}\text{Tc}$  with SPECT/CT exposes patients to ionizing radiation. Intraoperatively, use of  $^{99m}\text{Tc}$  only gives acoustic feedback and, with conventional gamma probes, is unable to provide real-time visual guidance. The 'long' radiotracer protocol (i.e. one day preoperative admission for SPECT/CT) can be logistically challenging (demanding a nuclear medicine unit with safety protocols for handling), time consuming, involving longer hospital stay, and leading to higher patient burden. Also,  $^{99m}\text{Tc}$  usage is costly, especially in combination with preoperative SPECT/CT. Although the combination with intraoperative use of blue dye is beneficial in terms of bilateral detection rate, in a

1  
2  
3     92 subset of patients blue dye is associated with allergic reactions, that may be severe (around 0.6%).(9, 10)  
4  
5     93 Common adverse effects related to blue dye are localized swelling or pruritus (2-4%), transient  
6  
7     94 discoloration of skin and urine (>95%) and a decrease in pulse oximetry readings due to colorimetric  
8  
9     95 interference.(11, 12)

10  
11     96 The aforementioned disadvantages contributed to the recent shift towards SLN mapping with  
12     97 indocyanine green (ICG).(13) ICG is a nonradioactive fluorescent dye that is visualised intraoperatively  
13  
14     98 with near-infrared (NIR) fluorescence imaging, providing real-time visual navigation. Recently, the FDA  
15  
16     99 approved ICG for the indication of lymphatic mapping in uterine and cervical cancers.(14) Compared to  
17  
18     100  $^{99m}\text{Tc}$ , ICG is non-radioactive, cheaper and logically more attractive. Compared to blue dye, ICG has a  
19  
20     101 better tissue penetration and a lower allergy risk. Overall, the use of ICG may lead to less burden on the  
21  
22     102 patient as its use enables shorter hospital admissions and injection under anaesthesia. (15-17) The  
23  
24     103 feasibility of ICG has been demonstrated and early reports showed ICG yields high SLN detection rates  
25  
26     104 in patients with early-stage cervical cancer.(18-21) Limitations of ICG include costs of NIR fluorescence  
27  
28     105 equipment and less guidance towards unexpected SLN positions because of the absence of preoperative  
29  
30     106 imaging. (22) Another pitfall is the tissue penetration of NIR fluorescence imaging of approximately 1  
31  
32     107 cm, meaning it can be detected through a centimetre of overlying tissue,(23) which is especially limiting  
33  
34     108 in patients with a high body mass index.(24, 25) Also, the small hydrodynamic diameter of the ICG  
35  
36     109 molecule may result in rapid spreading towards second and third echelon nodes,(16) undesirably leading  
37  
38     110 to higher number of removed (false) SLNs. Although clinically the shift towards ICG seems to be in  
39  
40     111 progress, shifting to an easy-to-use technique is not justified without prior evidence of its clinical  
41  
42     112 reliability and validity wherein it performs at least as good as the current standard of care.

43  
44     113 In both endometrial and cervical cancer adequately powered prospective trials comparing ICG with the  
45  
46     114 more conventional method of  $^{99m}\text{Tc}$  and blue dye are lacking.(26-29) The surgical practice has changed  
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48     115 rapidly towards ICG in absence of level A evidence on its diagnostic accuracy. The unexpected recent  
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50     116 findings of the LACC trial have again stressed the importance of compelling evidence before switching  
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52     117 to a new surgical technique.(30) Regarding cervical cancer, a prospective study by Lührs et al. compared  
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54     118 ICG with intraoperatively administered  $^{99m}\text{Tc}$  in 65 cervical cancer patients, without adding blue dye and  
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56     119 without performing preoperative SPECT/CT imaging. The researchers reported a significant higher  
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58     120 bilateral detection rate of ICG compared to  $^{99m}\text{Tc}$  without any significant improvement by combining the  
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60     121 two. The lack of preoperative imaging in this study possibly affected the bilateral detection rate of  $^{99m}\text{Tc}$   
   122 negatively, which was low at 60%.(31) The FILM trial, a randomised non-inferiority trial comparing ICG  
   123 with blue dye for SLN mapping in predominantly endometrial cancer (n=169; 96%) though also cervical  
   124 cancer (n=7; 4%), reported significantly higher SLN detection rates with ICG than with blue dye only.(29)

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3 125 Besides its limited applicability in cervical cancer, a second major limitation is the absence of a  
4 126 radiotracer, making a comparison between ICG and the conventional combined approach impossible.  
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7 127 Retrospective cohort studies reporting on the comparison of ICG versus  $^{99m}\text{Tc}$  combined with blue dye  
8 128 exist, but are generally of insufficient quality, underpowered and potentially suffer from publication bias.  
9 129 After a systematic review and meta-analysis of the available literature comparing ICG with  $^{99m}\text{Tc}$  and blue  
10 130 dye, we found that the pooled bilateral detection rate with ICG appeared to be significantly higher.(32)  
11 131 However, in adherence with the Grading of Recommendations, Assessment, Development, and  
12 132 Evaluation (GRADE) guidelines, the quality of evidence was too low to provide strong recommendations  
13 133 and directly omit the combined approach of a radiotracer and blue dye. In addition, all included studies  
14 134 reported a higher average number of identified SLNs when using ICG as a tracer, indicating these are  
15 135 not likely to be all SLNs but rather second echelon lymph nodes. Failing to excise the true SLN could  
16 136 result in missed lymph node metastases.  
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19 137 Before omitting any well-functioning and evidence based procedure ( $^{99m}\text{Tc}$  combined with blue dye)  
20 138 high quality evidence on the performance of ICG in cervical cancer SLN mapping is needed. In the FILM  
21 139 trial by Frumovitz et al. it was stated: "*Although the combination of blue dye and radiocolloid might be*  
22 140 *better than blue dye alone and equivalent to indocyanine green in detecting sentinel nodes, no studies –*  
23 141 *either prospective or retrospective – have compared the combination of blue dye and radiocolloid with*  
24 142 *indocyanine green.*".(29) With our study, we intend to perform the proposed prospective study  
25 143 comparing ICG with the combination of radiotracer and blue dye (including preoperative SPECT/CT) in  
26 144 early-stage cervical cancer patients. The presumed benefits of ICG are only valuable if its detection rate  
27 145 proves to be at least non-inferior to  $^{99m}\text{Tc}$  and blue dye.  
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## 40 146 Methods and analysis

### 41 147 42 148 Study design

43 149 The FluoreSENT study is initially designed as a prospective, multicentre, non-randomised, single-arm,  
44 150 cross-sectional study in which we compare two SLN methods in early-stage cervical cancer patients  
45 151 undergoing primary surgical treatment (FIGO stage IA – IB2 or IIA1): ICG with NIR fluorescence imaging  
46 152 versus  $^{99m}\text{Tc}$  (including preoperative SPECT/CT) and blue dye. The study started in July 2021 and is  
47 153 coordinated by the University Medical Center Utrecht (UMCU) and monocentric in the rollout phase. We  
48 154 plan to expand this study in other Dutch tertiary referral centres to increase the accrual rate. The planned  
49 155 end date of this study is July 2024.  
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3 157 Given that the current bilateral detection rate using  $^{99m}\text{Tc}$  combined with blue dye is already high (86%  
4 in own cohort) and the use of ICG has substantial benefits, a non-inferiority design is justified.(33) When  
5 non-inferiority is reached, a switch in standard care to ICG with NIR fluorescence imaging (i.e.  
6 abandoning  $^{99m}\text{Tc}$  and blue dye) is supported. It is important to note that this is not an equivalence trial.  
7  
8 160 When SLN mapping with ICG produces a higher bilateral detection rate than SLN mapping with  $^{99m}\text{Tc}$   
9 and blue dye, this is not considered a negative study result, whereas this is clearly a convincing reason  
10 to change the current practice. We chose bilateral detection rate as the primary endpoint because  
11 bilateral detection of SLNs has proven to decrease false negative rate and is thus considered to improve  
12 reliability and oncological safety.(4, 34) This protocol has been developed in line with research protocol  
13 template of the Central Committee on Research Involving Human Subjects (CCMO) and the SPIRIT  
14 recommendations.(35)  
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18 169 **Study population**  
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20 170 The subjects will be drawn from a population of patients with histopathologically proven primary  
21 malignancy of the cervix uteri. Patients are eligible to participate if they are planned for a (robot-assisted)  
22 laparoscopic or open SLN procedure as part of the standard surgical treatment for FIGO stage IA1-IB2  
23 or II A cervical cancer (according to the FIGO 2018 guidelines(36)), aged  $\geq 18$  years and able to provide  
24 informed consent. Exclusion criteria are: pregnancy or current breastfeeding, renal insufficiency stage 3  
25 or 4, prior allergic reaction to ICG,  $^{99m}\text{Tc}$  or patent blue, prior severe allergic reaction to iodine. Informed  
26 consent will be obtained before the start of any study activity.  
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30 178 **Sample size**  
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32 179 The sample size calculation was based on our own data and current literature. Data from our historical  
33 cohort showed a bilateral detection proportion of 86% (95% CI 80-91%) for SLN mapping with  $^{99m}\text{Tc}$  and  
34 blue dye (manuscript in preparation; (33)). The pooled proportion of bilateral detection rate of ICG was  
35 found to be between 89.4% and 91.5%, depending on how studies in the meta-analysis were handled  
36 (in preliminary analysis). Based on consensus discussion by clinicians in the study team and a  
37 comprehensive review of the literature, a non-inferiority margin of 0.05 was set. For assessing non-  
38 inferiority in paired proportions the asymptotic test statistic, which is the so-called Nam score test,  
39 or restricted maximum likelihood estimation (RMLE-based) test statistic was used.(37) The power and  
40 sample size was calculated in the statistical software package PASS (Power Analysis and Sample Size),  
41 verified for non-inferiority tests (one-sided) for two correlated proportions.(38) The calculations were  
42 checked by a statistician (power formula is provided in the PASS User's Guide(38)).  
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44 190 In conclusion, comparing a proportion ( $^{99m}\text{Tc}$  and blue dye at 0.86, ICG 0.89) in one sample with a non-  
45 inferiority margin of 0.05, with a Type I error ( $\alpha$ ) set at 0.05, Type II error ( $\beta$ ) set at 0.2 (power  $1-\beta = 0.8$ ),  
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3 192 and Nuisance set at 0.12 (based on the proportion of discordant pairs), we require a sample size of 101  
4 193 cases. The complete list of parameters used for the power calculation is provided in Appendix 1.  
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7 194 **Investigational product**  
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10 195 ICG is a fluorescent agent used for diagnostic purposes in adults and children with a benign safety  
11 196 profile. One of the diagnostic purposes is fluorescence imaging of lymph nodes and delineation of  
12 197 lymphatic vessels in the cervix and uterus in patients with solid tumours during lymphatic mapping. No  
13 198 therapeutic effects are expected. ICG (VERDYE 25mg, Diagnostic Green GmbH, Germany) is registered  
14 199 for diagnostic purposes in adults under Dutch RVG number 31052.  
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19 200 Allergic reactions and anaphylactic shocks due to ICG were reported in very rare (<0.01%) cases. In  
20 201 patients with renal insufficiency, the risk of anaphylactic shock appears to be higher. In very rare cases  
21 202 spasms of the coronary arteries are described. Radioactive iodine uptake studies should not be  
22 203 performed for at least a week following the use of ICG. No other complications or potential risks of ICG  
23 204 are reported.(14)  
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28 205 **Trial intervention**  
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30 206 The flowchart in **Figure 1** presents a schematic overview of the study design. All subjects undergo a SLN  
31 207 procedure as part of the surgical treatment and receive ICG injection in adjunct to the current combined  
32 208 approach. Subjects will be preoperatively injected with  $^{99m}\text{Tc}$  followed by a SPECT/CT 90-120 minutes  
33 209 post-injection (according to current standard-of-care).(33) The surgeon (gynaecological oncologist) will  
34 210 not consult the SPECT/CT preoperatively (secured by automated logging of consultation). At the start of  
35 211 surgery, subjects are injected with four millilitres of ICG 1.25 mg/ml (study procedure) and four millilitres  
36 212 of blue dye (standard-of-care) under general anaesthesia; 1 ml of both tracers into each quadrant of the  
37 213 cervix. During surgery the SLNs will be first identified with NIR fluorescence light using FireFly fluorescent  
38 214 imaging system (Intuitive Surgical Inc.) in robotic surgery or a CE marked NIR fluorescence platform  
39 215 applicable to laparoscopic or laparotomic surgery; in this light NIR fluorescent nodes will light up green  
40 216 (**Figure 2**). Localisation of each NIR fluorescent SLN will be reported. When the NIR fluorescent SLN(s)  
41 217 are identified, the gynaecological oncologist will check the SLN(s) for radioactivity with a gamma probe  
42 218 (either *in vivo* or *ex vivo*) and blue colour. When completed, the procedure is repeated in the  
43 219 contralateral hemipelvis. Results are reported as follows: of each SLN the localisation is reported  
44 220 according to a standardised format (see Appendix 2) and it is stated if detected with NIR fluorescence  
45 221 (ICG), radioactivity ( $^{99m}\text{Tc}$ ) and/or blue colour (blue dye). All SLNs identified are excised. After finishing  
46 222 this procedure bilaterally, the surgeon consults the SPECT/CT (time of deblinding is logged both  
47 223 automatically and manually) and reports whether radioactive node(s) on SPECT/CT correspond to the  
48 224 excised SLN(s). To prevent missing SLNs, the pelvic site will be checked for residual radioactive nodes  
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3 225 and blue nodes, and excised, if present. Residual radioactivity of the surgical site will be measured and  
4 226 deemed negative if background counts are less than 10% of the maximum SLN count.  
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7 227 Blue dye and ICG are injected sequentially, before entering the retroperitoneal space. Previous studies  
8 228 using a combined injection of patent blue and ICG experienced no clotting of the two dyes, both at  
9 229 macroscopic and microscopic level.(39-41) To prevent from bias in detection of SLNs, injecting blue dye  
10 230 in a later stage of surgery – i.e. after SLN mapping with ICG and NIR fluorescence is completed – has  
11 231 been explored. However, starting SLN mapping with ICG would result in anatomical structures and  
12 232 lymphatic vessels that have already been destructed. Because of the destructed lymph vessels, injecting  
13 233 blue dye in a later stage would underestimate the true benefit as the dye will not reach the lymph nodes.  
14 234 This intrapatient study design is thereby limited by the inability of blinding for the outcome of blue dye.  
15 235 Except for injection of ICG and detection with NIR fluorescence imaging while blinded for the assessment  
16 236 of the SPECT/CT, the complete treatment is maintained according to the current standard-of-care.  
17 237 Intraoperative recordings and pictures can be made for retrospective tumour-to-background ratio  
18 238 analysis. All follow-up visits take place according to the national guidelines. There is no special follow-  
19 239 up required for subjects in this study. Subjects are asked to fill in the IN-PATSAT32 questionnaire  
20 240 postoperatively, developed by European Organisation for Research and Treatment of Cancer (EORTC),  
21 241 for assessing patients' perception of the quality of hospital-based care (not mandatory).  
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### 32 242 **Outcomes**

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35 243 The primary outcome is bilateral detection rate of SLNs with ICG and NIR fluorescence imaging versus  
36 244  $^{99m}\text{Tc}$  (including pre-operative SPECT/CT) and blue dye. SLN is defined as the first lymph node(s) of each  
37 245 hemipelvis to receive afferent lymphatic drainage from the primary cervical tumour, identified by either  
38 246 ICG, gamma radiation using  $^{99m}\text{Tc}$  or blue dye. Bilateral detection is defined as number of patients  
39 247 detected with at least one SLN in each hemipelvis.  
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42 248 Secondary outcomes include: (1) overall (i.e. at least unilateral) detection rate, sensitivity and false  
43 249 negative rate (FNR) of ICG and  $^{99m}\text{Tc}$  and blue dye, with pelvic lymph node dissection (PLND) as the  
44 250 reference standard to confirm tumour positive lymph nodes (part of current standard-of-care); (2)  
45 251 correlation between NIR fluorescent, radioactive (both intraoperative and with SPECT/CT) and blue  
46 252 stained SLNs in terms of anatomical location; (3) adverse events of ICG,  $^{99m}\text{Tc}$  and blue dye; (4) time to  
47 253 complete SLN detection with ICG versus  $^{99m}\text{Tc}$  and blue dye; (5) cost-effectiveness comparison (cost of  
48 254 procedure versus yielded bilateral detection rate) of ICG versus  $^{99m}\text{Tc}$  and blue dye SLN detection; (6)  
49 255 surgical evaluation of NIR fluorescent imaging (usability) measured with two short questionnaires  
50 256 tailored for the surgeons; and (7) patient satisfaction with the oncological care and procedure measured  
51 257 with the validated EORTC IN-PATSAT32 questionnaire.  
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3 258 The basic clinical, surgical and histopathological parameters will be recorded, including: age at diagnosis,  
4 259 body mass index (BMI, in kg/m<sup>2</sup>), history of abdominal surgery, ASA classification (American Society of  
5 260 Anaesthesiologists), FIGO stage (2018), type of procedure, tumour histology and size, lymph vascular  
6 261 space invasion (LVSI), nodal count and status, parametrial involvement, vaginal involvement, positive  
7 262 resection margins, and adjuvant or adjusted treatment (the latter due to intraoperative finding of  
8 263 positive lymph nodes). Subanalysis will evaluate if these parameters are possible confounders or effect  
9 264 modifiers.  
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19 266 **Data collection and management**  
20 267 All measurements will be systematically recorded using an electronic Clinical Report Form (eCRF) build  
21 268 in Castor Electronic Data Capture (EDC) system. Data will be collected in coded form and monitored by  
22 269 data managers from the UMC Utrecht. Baseline characteristics are collected pseudonymously from the  
23 270 medical records in consultation with the data management department of the research centre(s). All  
24 271 study procedures at the research centre(s) are monitored by an independent monitor during multiple  
25 272 visits according to a specified protocol.  
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29 273 The principal investigators at the research centre(s) bear responsibility for safe data handling. After the  
30 274 project is finished, data will be stored for 25 years according to the current Medical Research Involving  
31 275 Human Subjects Act (WMO). Handling of personal data will comply with the EU General Data Protection  
32 276 Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.  
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36 277 **Adverse events**  
37 278 Adverse events are defined as any undesirable experience occurring to a subject during the study,  
38 279 whether or not considered related to the intervention (SLN mapping with ICG and NIR fluorescence). All  
39 280 adverse events reported spontaneously by the subject or observed by the investigator or his staff will be  
40 281 recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs in the  
41 282 48 hours following the SLN procedure. The sponsor will report the SAEs through the Dutch web portal  
42 283 ToetsingOnline to the accredited MREC that approved the protocol, within 7 days of first knowledge for  
43 284 SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete  
44 285 the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after  
45 286 the sponsor has first knowledge of the serious adverse events.  
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54 287 **Statistical analysis**  
55 288 We will perform a comparison (single sample) of two diagnostic modalities and aim to assess non  
56 289 inferiority (note: not equivalence) of the ICG SLN mapping in terms of bilateral detection rate. Our  
57 290 analysis is based on previous literature on non-inferiority for paired binary data.(37) Statistical software  
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3 291 programs SPSS and R will be used to perform the analyses. The measured primary endpoint is the  
4 292 proportion of bilateral SLN detection which is tested in a paired setting. The null(H0) and alternative(H1)  
5 293 hypotheses for this non-inferiority study are as follows:  
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9 294 • *H0*: SLN mapping with ICG is inferior to SLN mapping with  $^{99m}\text{Tc}$  and blue dye with respect to  
10 295 the proportion of bilaterally detected sentinel nodes.  
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12 296 • *H1*: SLN mapping with ICG is non-inferior to SLN mapping with  $^{99m}\text{Tc}$  and blue dye with respect  
13 297 to the proportion of bilaterally detected sentinel nodes.  
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17 299 The analysis of all outcome data will be performed using intrapatient comparison (McNemars test).  
18 300 Categorical and continuous data will be presented in a quantitative way. The bilateral detection rates of  
19 301 ICG,  $^{99m}\text{Tc}$  and blue dye are presented separately with corresponding 95% confidence intervals.  
20  
21 302 Categorical data will be analysed using the Fisher Exact or Chi-square, as appropriate. For continuous  
22 303 outcomes t-test will be used in case of normally distributed data. If not normally distributed, Mann-  
23 304 Whitney-U test will be performed. Besides 95% confidence intervals, p-values will be reported with a  
24 305 value of <0.05 considered significant.  
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28 306 In case of identified inconsistencies or missing data, additional source documents will be requested from  
29 307 the study site to resolve ongoing inconsistencies. If necessary, patients are called to resolve missing data.  
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31 308 If missing data restrict further analysis, multiple imputation analyses will be conducted.  
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35 309 **Patient and public involvement**  
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38 310 Members of patient organisation Stichting Olijf were involved in the design of this study.  
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41 311 **Ethics and dissemination**  
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44 312 This current study was approved by Institutional Review Board and Medical Research Ethics Committee  
45 313 Utrecht (number 21-014) in accordance with the Dutch Medical Research Involving Human Subjects Act  
46 314 (WMO) and other applicable Dutch and European guidelines, regulations and Acts. The study was  
47 315 registered in the Netherlands Trial Register (number NL9011). All subjects will have to sign and date  
48 316 written informed consent. No study activities will occur prior to obtaining consent. Subjects retain the  
49 317 right to withdraw at any point for any reason.  
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53 318 This study has been assessed as a low risk study. ICG is given in adjunct to the current standard of care  
54 319 and subjects are not withheld of any type of standard treatment. Risks associated with participation can  
55 320 be considered negligible. Participating in this study will be associated with minor discomfort and might  
56 321 be beneficial for individuals, as mapping with ICG might result in higher SLN detection rates (based on  
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3 322 previous literature). This study intends to improve oncological care and prognosis for all early-stage  
4 323 cervical cancer patients.

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6 324 We will ensure our findings and the acquired knowledge will be transferred to clinicians and researchers  
7 325 in the field. Findings arising from this study will be published at national and international conferences.  
8 326 The final manuscript will be submitted for publication to an open access peer-reviewed scientific journal.  
9 327 Both positive and negative trial results will be disclosed. Results will also be updated in the Netherlands  
10 328 Trial Register, which is the primary registry for the Netherlands and recognized and accepted by the  
11 329 WHO and ICMJE. Subjects and cervical cancer patients will be informed about the study results by the  
12 330 newsletter and social media accounts of patient organisation Stichting Olijf.

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14 331  
15 332 **Author contributions**

16  
17 333 IGT Baeten: Conceptualization, Methodology, Writing – Original Draft, Visualization.  
18  
19 334 JP Hoogendam: Conceptualization, Methodology, Writing - Original Draft, Validation (as  
20 335 epidemiologist and fellow gynaecological oncology).  
21  
22 336 AJAT Braat: Methodology, Validation (as radiologist with expertise in nuclear medicine and use of  
23 337 technetium-99m SPECT/CT imaging), Writing - Review & Editing.  
24  
25 338 WB Veldhuis: Validation (as radiologist with expertise in gynaecologic oncology), Writing - Review &  
26  
27 339 Editing.  
28  
29 340 GN Jonges: Validation (as pathologist with expertise in pathological assessment of SLNs and cervical  
30 341 cancer), Writing - Review & Editing.  
31  
32 342 IM Jürgenliemk-Schulz: Validation (as radiation oncologist with expertise in cervical cancer treatment),  
33  
34 343 Writing - Review & Editing.  
35  
36 344 RP Zweemer: Conceptualization, Methodology, Validation (as gynaecological oncologist), Writing -  
37  
38 345 Review & Editing.  
39  
40 346 CG Gerestein: Conceptualization, Methodology, Validation (as gynaecological oncologist), Writing -  
41  
42 347 Review & Editing, Supervision.

43  
44 348  
45 349 **Funding statement**

46  
47 350 In the set-up and rollout phase this (monocentre) research received no specific grant from any funding  
48  
49 agency in the public, commercial or not-for-profit sectors. In order to expand this study to other Dutch  
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51 tertiary centres we are applying for funding within the public sector. If the application is granted, we will  
52  
53 ensure that the funder is not going to be involved in collection, management, analysis and interpretation  
54  
55 of data, writing of the manuscript and decision to submit the manuscript for publication, nor does it  
56  
57 have authority over the publications.  
58  
59 355  
60 356

**357 Competing interests**

358 RZ is a proctor for robot-assisted surgery in gynaecological oncology on behalf of Intuitive Surgical Inc.  
359 All other authors declare no conflicts of interest.

**360**  
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**508 Figure legends**

509 **Figure 1.** Flowchart of study procedures. Blue boxes represent the current standard of care; red boxes  
510 represent the study specific procedures.

511 **Figure 2.** Fluorescence guided surgery showing lymphatic vessels (left) and sentinel lymph node (right).

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ICG = Indocyanine Green

NIR = Near-infrared

 $^{99m}\text{Tc}$  = Technetium-99m nanocolloid

Blue dye = patent blue

SLN(s) = Sentinel Lymph Node(s)

06182013  
18 September 2022. Downloaded from <http://bmjopen.bmjjournals.org/>

Surgeons blinded for assessment  
SPECT-CT

Identification of **NIR fluorescent**  
SLN(s)  
- Report localisation of SLN(s)  
- Evaluation of radioactivity and blue  
dye *in vivo*  
- Excision of SLN(s)

Identification of residual **radioactive**  
SLN(s)  
- Report localisation of residual SLN(s)  
- Evaluation of NIR fluorescence and  
blue dye *in vivo*  
- Excision of SLN(s)

Identification of residual **blue** SLN(s)  
- Report localisation of residual SLN(s)  
- Evaluation of NIR fluorescence and  
radioactivity *in vivo*  
- Excision of SLN(s)

## One day preoperative

- Injection of  $^{99m}\text{Tc}$
- SPECT-CT 90 minutes post-injection

## Day of surgery

Start of (robot-assisted) laparoscopy  
or laparotomy

Injection of **blue dye** into 4 quadrants

Injection of **ICG** into 4 quadrants

*Start surgery*

Identification of **NIR fluorescent**  
(ICG positive) SLNs

*Consultation of SPECT-CT*

Identification of any residual  
**radioactive** ( $^{99m}\text{Tc}$  positive) SLNs

Identification of any residual **blue**  
SLNs

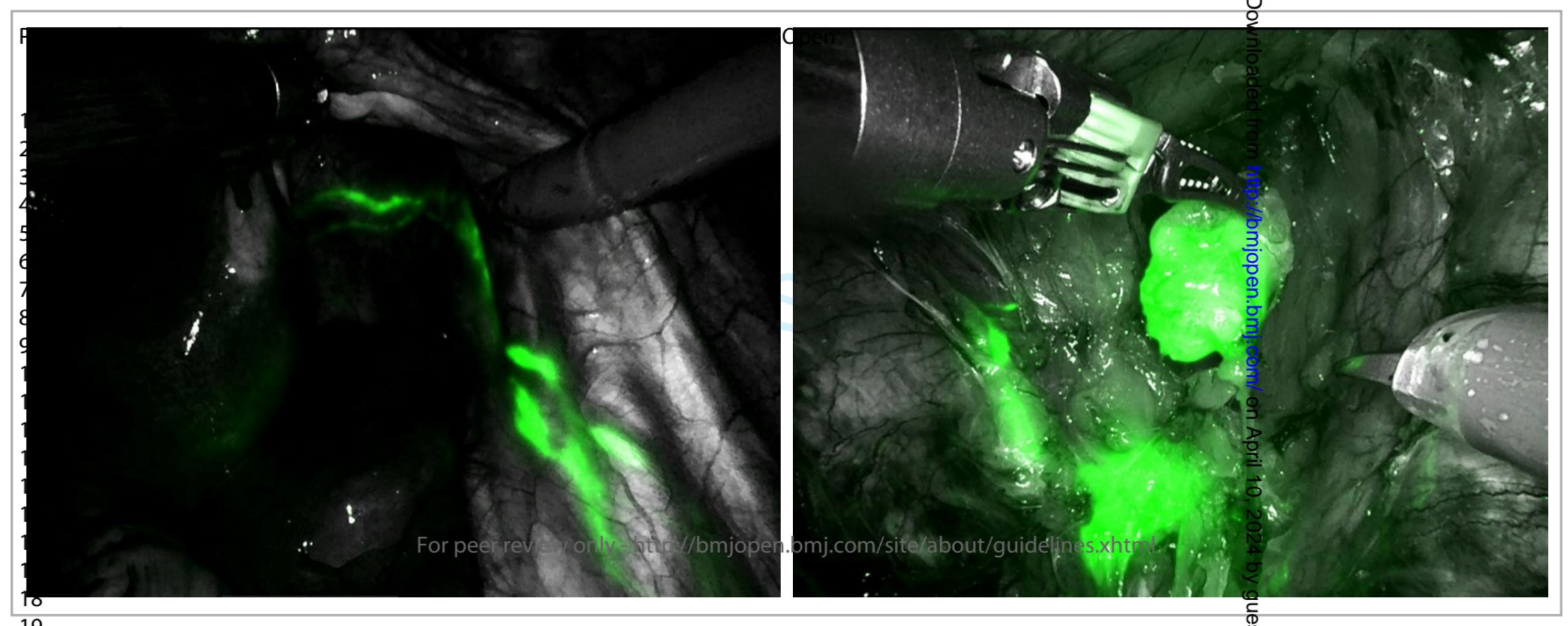
Pelvic lymph node dissection

*Using the NIR fluorescence camera*

*Using the gamma probe*

*Sent all SLNs for frozen section  
analysis*

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## Appendix 1

### Sample size calculation

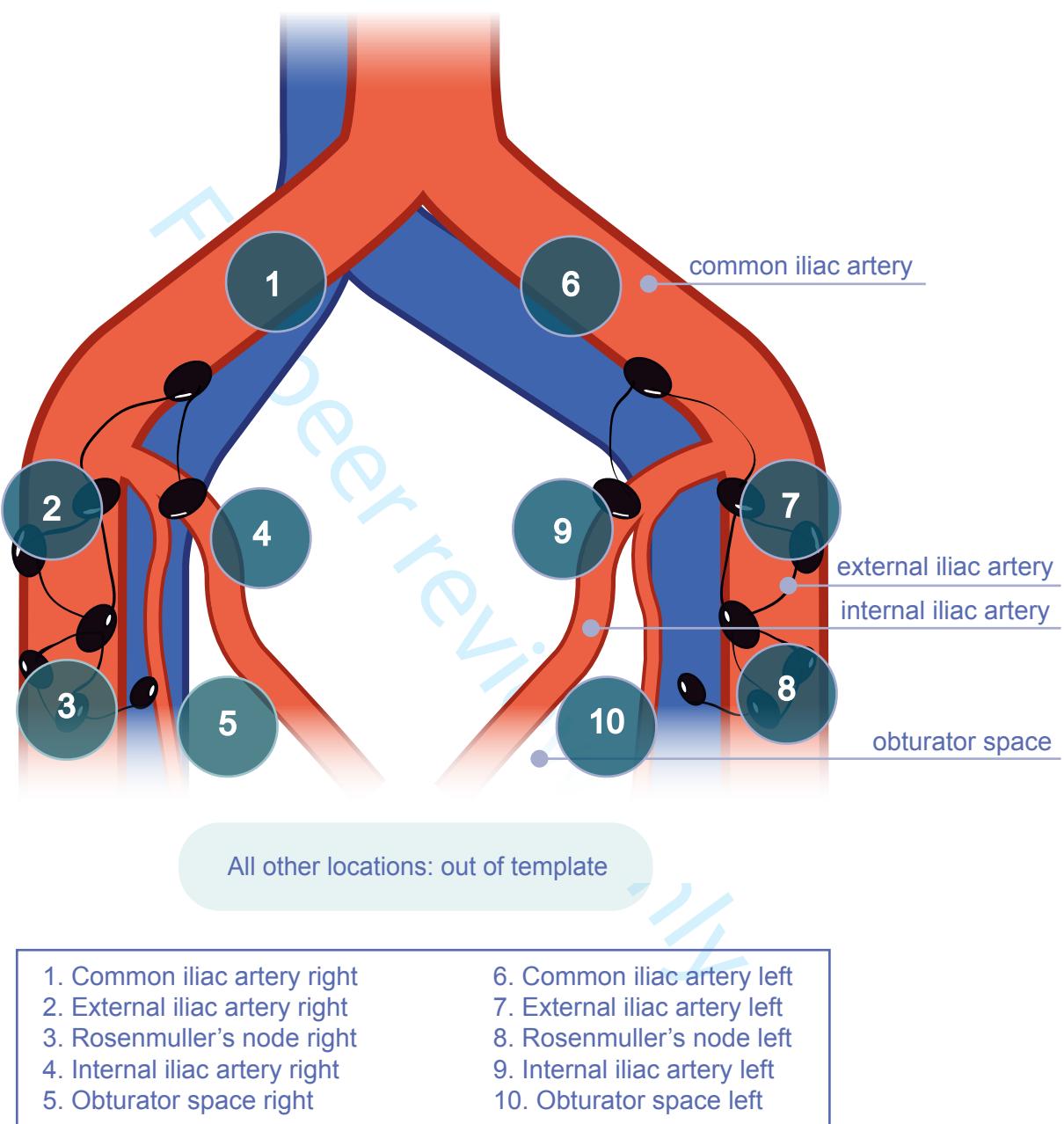
For assessing non-inferiority in paired proportions we will use an asymptotic test statistic, which is the so-called Nam score test, or restricted maximum likelihood estimation (RMLE-based) test statistic.<sup>(1)</sup> The power and sample size was calculated in the statistical software package PASS (Power Analysis and Sample Size), verified for non-inferiority tests (one-sided) for two correlated proportions.<sup>(2)</sup> The calculations were checked by a statistician (the power formula is given in the PASS User's Guide).

We set the following parameters in PASS based on consensus discussion by the clinicians in our study team and a comprehensive review of the aforementioned literature:

- *Power* is the probability of rejecting a false null hypothesis. Set at 0.80.
- *Equivalence Difference (De)* is the maximum difference between the two proportions that is still called 'equivalent.' Set at 0.05 (equal to the non-inferiority margin).
- *Actual Difference (Da)* is the actual difference between Pt and Ps. That is, Da = Pt-Ps. Set at 0.03.
- *Treatment Proportion (Pt)* is the response proportion to the treatment (experimental or new) test. Set at 0.89.
- *Standard Proportion (Ps)* is the response proportion to the standard (reference or old) test. Set at 0.86.
- The *Nuisance Parameter* is a value that is needed, but is not a direct part of the hypothesis. The parameter is based on the proportion of discordant pairs. Set at 0.12.
- *Alpha ( $\alpha$ )* is the probability of rejecting a true null hypothesis. Set at 0.05.
- *Beta ( $\beta$ )* is the probability of accepting a false null hypothesis. Set at 0.20

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item No	Item	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <b>Manuscript page 1</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <b>Netherlands Trial Registry: number NL9011 (see Page 2).</b>
	2b	All items from the World Health Organization Trial Registration Data Set <b>For the Netherlands the NTR is the Primary Registry accepted by the WHO and ICMJE.</b>
Protocol version	3	Date and version identifier <b>01-07-2021 / NL75722.041.20 / version 1.4</b>
Funding	4	Sources and types of financial, material, and other support <b>Funding, manuscript page 11</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <b>Check (described on title page of study protocol)</b>
	5b	Name and contact information for the trial sponsor <b>Check; UMC Utrecht (described in study protocol)</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <b>Check (described in study protocol)</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <b>Check (described in study protocol)</b>

**Introduction**

1	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <b>Introduction, manuscript page 3 - 5</b>
2		6b	Explanation for choice of comparators <b>Introduction, manuscript page 3 – 5</b>
3	Objectives	7	Specific objectives or hypotheses <b>Introduction, page 3 – 5, and Statistical analysis, manuscript page 10</b>
4	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <b>Methods, Study design, manuscript page 5</b>

## Methods: Participants, interventions, and outcomes

1	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <b>Methods, Study population, manuscript page 5</b>
2	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <b>Methods, Study design and Study population, manuscript page 5-6</b>
3	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <b>Methods, manuscript page 7</b>
4		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <b>Not applicable</b>
5		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <b>Not applicable</b>
6		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <b>Methods, Trial intervention, manuscript page 7</b>

1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <a href="#">Methods, Outcomes, manuscript page 8</a>
11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <a href="#">See flow chart in Figure 1 of the manuscript</a>
17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <a href="#">Methods, Sample size, manuscript page 6</a>
22	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <a href="#">Check (recruitment and informed consent procedure are described in study protocol)</a>

### 28 Methods: Assignment of interventions (for controlled trials)

#### 30 Allocation:

32	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions <a href="#">Not applicable</a>
41	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned <a href="#">Not applicable</a>
49	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions <a href="#">Not applicable</a>
53	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Not applicable</a>

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- 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial  
**Not applicable**

## Methods: Data collection, management, and analysis

- Data collection methods    18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol  
**Methods, Data collection and management, manuscript page 9**
- 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  
**Not applicable**
- Data management    19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol  
**Methods, Data collection and management, manuscript page 9. Also, there is a reference to Datamanagement plan in study protocol.**
- Statistical methods    20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  
**Methods, Statistical analysis, manuscript page 10**
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)  
**Methods, Statistical analysis, manuscript page 10**
- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)  
**Check (handling missing data is described in study protocol).**

## Methods: Monitoring

- Data monitoring    21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol.  
Alternatively, an explanation of why a DMC is not needed  
**Methods, Data collection and management, manuscript page 9.**  
**Independent monitor has been assigned.**

1	21b	Description of any interim analyses and stopping guidelines, including 3 who will have access to these interim results and make the final 4 decision to terminate the trial  5 Not applicable
6	Harms	22 Plans for collecting, assessing, reporting, and managing solicited and 7 spontaneously reported adverse events and other unintended effects 8 of trial interventions or trial conduct  9 Check (described in study protocol according to the CCMO 10 guidelines)
11	Auditing	23 Frequency and procedures for auditing trial conduct, if any, and 12 whether the process will be independent from investigators and the 13 sponsor  14 Check (reference to written monitor plan in protocol)
<b>Ethics and dissemination</b>		
15	Research ethics approval	24 Plans for seeking research ethics committee/institutional review board 16 (REC/IRB) approval  17 Approval has been obtained.
18	Protocol amendments	25 Plans for communicating important protocol modifications (eg, 19 changes to eligibility criteria, outcomes, analyses) to relevant parties 20 (eg, investigators, REC/IRBs, trial participants, trial registries, journals, 21 regulators)  22 Check (described in study protocol according to the CCMO 23 guidelines)
24	Consent or assent	26a Who will obtain informed consent or assent from potential trial 25 participants or authorised surrogates, and how (see Item 32)  26 Check (recruitment and informed consent procedure are described 27 in study protocol)
28		26b Additional consent provisions for collection and use of participant data 29 and biological specimens in ancillary studies, if applicable  30 Not applicable
31	Confidentiality	27 How personal information about potential and enrolled participants will 32 be collected, shared, and maintained in order to protect confidentiality 33 before, during, and after the trial  34 Check (reference to written Datamanagement plan in study protocol)
35	Declaration of interests	28 Financial and other competing interests for principal investigators for 36 the overall trial and each study site  37 Competing interests, manuscript page 12
38	Access to data	29 Statement of who will have access to the final trial dataset, and 39 disclosure of contractual agreements that limit such access for 40 investigators  41 Check (reference to written Datamanagement plan in study protocol)

- 1 Ancillary and  
2 post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for  
3 compensation to those who suffer harm from trial participation  
4 **Check (liability insurance and participant insurance are taken out by  
5 the study sponsor)**
- 6 Dissemination  
7 policy 31a Plans for investigators and sponsor to communicate trial results to  
8 participants, healthcare professionals, the public, and other relevant  
9 groups (eg, via publication, reporting in results databases, or other  
10 data sharing arrangements), including any publication restrictions  
11 **Check (written Dissemination plan)**
- 12 31b Authorship eligibility guidelines and any intended use of professional  
13 writers  
14 **Check**
- 15 31c Plans, if any, for granting public access to the full protocol, participant-  
16 level dataset, and statistical code  
17 **Check (reference to written Datamanagement plan in study protocol)**

## 23 Appendices

- 24 Informed consent 32 Model consent form and other related documentation given to  
25 materials participants and authorised surrogates  
26 **Check (added the MREC approved model as supplementary file)**
- 27 Biological 33 Plans for collection, laboratory evaluation, and storage of biological  
28 specimens specimens for genetic or molecular analysis in the current trial and for  
29 future use in ancillary studies, if applicable  
30 **Not applicable**

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

# Informatie voor deelname aan medisch-wetenschappelijk onderzoek

## Een nieuwe techniek voor het opsporen van schildwachtklieren

**Officiële titel:** De bilaterale schildwachtklier detectie van fluorescent indocyanine groen in vergelijking met technetium-99m en blauw in de schildwachtklierprocedure in stadium I-IIA cervixcarcinoom: de FluoreSENT studie

### Inleiding

Beste mevrouw,

U krijgt deze brief omdat er bij u baarmoederhalskanker is gevonden. Er komt nu ongetwijfeld veel op u af. Toch hopen we dat u tijd wil maken voor het lezen van deze informatiebrief over meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig.

U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Lees de informatie rustig door. Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage C.

### Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, professor Ruurda.
- Lees de informatie op [www.rijksoverheid.nl/mensenonderzoek](http://www.rijksoverheid.nl/mensenonderzoek).

### 1. Algemene informatie

Het UMC Utrecht heeft dit onderzoek opgezet. Hieronder noemen we het UMC Utrecht steeds de 'opdrachtgever'. De onderzoekers, dit zijn artsen en onderzoeksverpleegkundigen, voeren het onderzoek uit. Voor dit onderzoek zijn in totaal 101 vrouwen met baarmoederhalskanker nodig. De medisch-ethische toetsingscommissie Utrecht heeft dit onderzoek goedgekeurd.

### 2. Wat is het doel van het onderzoek?

U krijgt binnenkort een operatie voor de behandeling van baarmoederhalskanker. De schildwachtklierprocedure is hier een onderdeel van. Dit houdt in dat de lymfeklieren die als eerste aansluiten op de tumor verwijderd worden om zeker te weten dat daar geen uitzaaiingen in zitten. Deze lymfeklieren worden ook wel schildwachtklieren genoemd. De schildwachtklieren kunnen opgespoord worden door bepaalde stoffen in te spuiten rond de tumor. Deze stoffen 'kleuren' de schildwachtklieren, zodat de arts kan zien waar de schildwachtklieren zitten. Er zijn verschillende technieken voor het 'kleuren' van de schildwachtklier beschikbaar.

In dit onderzoek bekijken we de werking van een nieuwe techniek voor het opsporen van de schildwachtklieren. We vergelijken de nieuwe techniek met de techniek die we nu gebruiken om zo te beoordelen welke de beste is.

### 3. Wat is de achtergrond van dit onderzoek?

Welke techniek gebruiken we nu voor het opsporen van schildwachtklieren?

Bij de huidige techniek spuit de arts een licht radioactieve stof in rondom de tumor. Hierna krijgt u een scan. Dit gebeurt meestal al één dag voor de operatie. Tijdens de operatie spuit de arts ook nog een blauwe kleurstof in. Beide stoffen maken de schildwachtklieren herkenbaar tijdens de operatie. De blauwe kleurstof kleurt soms het gezicht en meestal de urine tot enkele dagen na de operatie blauw. Ook kan de blauwe kleurstof een allergische reactie veroorzaken in iets minder dan 1 op de 100 gevallen.

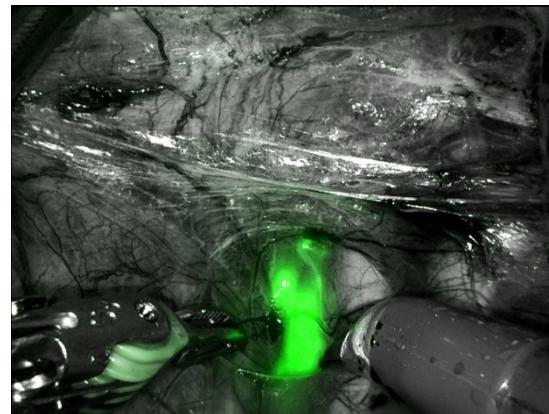
Bij deze schildwachtklierprocedure wordt straling gebruikt. Er bestaat een kleine kans dat de gebruikte straling leidt tot schade aan uw gezondheid. De schildwachtklierprocedure is standaard bij de behandeling van uw ziekte. Er is daarom bij deelname aan dit onderzoek geen extra risico door straling.

Welke nieuwe techniek gaan we onderzoeken?

Bij de nieuwe techniek wordt een groene stof ingespoten rondom de tumor. Dit gebeurt tijdens de operatie als u slaapt. De groene stof is niet zichtbaar met het blote oog, maar wel met een speciale camera. Wanneer deze camera wordt gebruikt, lichten de schildwachtklieren groen op. Op het plaatje hiernaast is te zien hoe dit eruit ziet.

Deze nieuwe techniek heeft voordelen. Zo wordt er geen straling gebruikt. Ook zijn allergische reacties zeer zeldzaam. De nieuwe techniek is minder belastend omdat een patiënt niet één dag voor de operatie al opgenomen moet worden in het ziekenhuis. We gaan onderzoeken of deze nieuwe techniek even goed werkt als de huidige techniek voor het vinden van de schildwachtklieren. Als dat zo is, dan kan deze nieuwe techniek de huidige techniek vervangen.

De groene stof is in Nederland nog niet geregistreerd voor het opsporen van schildwachtklieren. Er is wel al veel ervaring met deze stof. Zo wordt de groene stof al lange tijd gebruikt bij operaties aan bijvoorbeeld de ogen of de lever. Ook zijn er veel onderzoekers geweest die deze groene stof al veilig hebben gebruikt voor het opsporen van schildwachtklieren bij andere soorten kanker.



### 4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?

Doet u mee met het onderzoek? Dan kost dat u geen extra tijd. Het onderzoek vindt plaats tijdens de standaard behandeling.

Stap 1: bent u geschikt om mee te doen?

De gegevens van de afspraak met uw arts en de uitslagen van alle standaardonderzoeken hebben bepaald dat u geschikt bent om mee te doen aan dit onderzoek.

Stap 2: hoe verloopt de operatie?

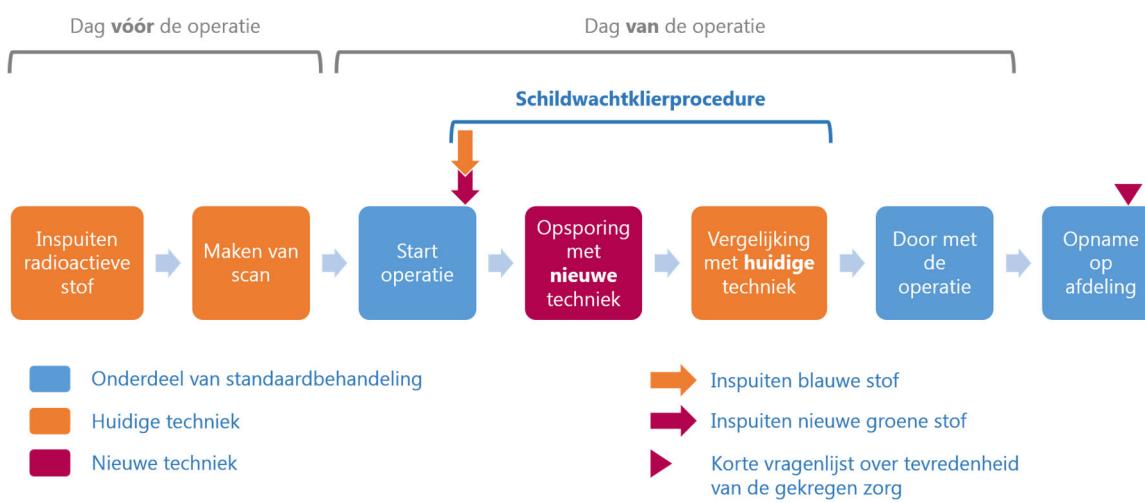
Als u meedoet aan dit onderzoek, gebruikt uw arts de nieuwe techniek voor het opsporen van de schildwachtklieren. Daarnaast gebruikt uw arts ook nog de huidige techniek. Hierdoor kan de werking van beide technieken worden vergeleken.

De groene stof is onderdeel van de nieuwe techniek. Deze stof wordt ingespoten als u onder narcose bent. Tijdens de operatie wordt een speciale camera gebruikt om de schildwachtklieren

1  
2  
3  
4  
5  
6  
7 op te sporen. U zult hier niets van merken. Verder verloopt de operatie zoals gebruikelijk is in uw  
8 ziekenhuis.  
9  
10  
11  
12

#### 13 **Stap 3: wat gebeurt er na de operatie?**

14 De zorg na de operatie blijft zoals die nu is. Er zijn geen extra controles nodig. Wel vragen we u  
15 één keer een vragenlijst in te vullen. Dit mag tijdens uw opname in het ziekenhuis of wanneer u  
16 weer thuis bent. Deze vragenlijst gaat over hoe u de zorg rondom de operatie heeft ervaren. De  
17 uitkomsten helpen ons om de behandeling en de zorg van baarmoederhalskanker verder te  
18 verbeteren.  
19  
20 In het plaatje hieronder ziet u het verloop van dit onderzoek.  
21  
22



## 34 **5. Welke afspraken maken we met u?**

35 We willen graag dat het onderzoek goed verloopt. Daarom maken we de volgende  
36 afspraken met u:

- 37 U bespreekt met uw arts of de onderzoeker als u nog aan een ander medisch-  
38 wetenschappelijk onderzoek wil meedoen;
- 39 U kan de week na de schildwachtklierprocedure geen schildkliertesten ondergaan.  
40 De reden hiervoor is dat er jodium in de groene stof zit. Dit kan de schildkliertest  
41 beïnvloeden.
- 42 U neemt contact op met de onderzoeker in deze situaties:
  - 43 U wordt in een ziekenhuis opgenomen;
  - 44 U krijgt plotseling problemen met uw gezondheid;
  - 45 U wilt niet meer meedoen met het onderzoek;
  - 46 Uw telefoonnummer, adres of e-mailadres verandert.

## 51 **6. Van welke bijwerkingen of nadelige effecten kunt u last krijgen?**

52 Het gebruik van de nieuwe techniek kent geen bijwerkingen. Wel kan er in zeldzame gevallen  
53 een allergische reactie optreden. Een allergische reactie op de groene stof komt minder dan 1  
54 op de 10.000 keer voor.

55 Wij verzoeken u onmiddellijk contact opnemen met de onderzoeker als u last krijgt van een  
56 allergische reactie. De klachten hiervan kunnen zijn: verhoogde hartslag, kortademigheid,  
57 opzwellingen van het gezicht, duizeligheid, misselijkheid, pijn in de borststreek, rusteloosheid,  
58 gevoel van warmte, jeuk, galbulten en/of blozen. De meeste allergische reacties treden op  
59 binnen enkele minuten of enkele dagen. Dat betekent dat u dan nog op de operatiekamer of  
60 de verpleegafdeling bent. In dat geval zijn er altijd zorgverleners in de buurt als u een

1  
2 allergische reactie krijgt.  
3  
4

## 5 **7. Wat zijn de voordelen en nadelen van meedoen aan het onderzoek?** 6

7 Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op  
8 een rij. Denk hier goed over na, en praat erover met anderen.  
9

10 U heeft een mogelijk voordeel van meedoen. Met de extra groene stof kunnen we de  
11 schildwachtklieren mogelijk makkelijker opsporen, maar dat is niet zeker. Met uw deelname  
12 helpt u mee in de zoektocht naar een betere schildwachtklierprocedure voor vrouwen met  
13 baarmoederhalskanker.

14 Een nadeel van meedoen aan het onderzoek is dat de duur van de operatie ongeveer 15  
15 minuten langer kan zijn. Dat is maar een klein deel van de totale duur van de operatie van  
16 ongeveer vier uur. De risico's van langere narcose zijn zeer laag. U kunt ook last krijgen van  
17 een allergische reactie op de nieuwe techniek, zoals beschreven in paragraaf 6.  
18

### 19 *Wilt u niet meedoen?* 20

21 U beslist zelf of u meedoet aan het onderzoek. Wilt u niet meedoen? Dan ondergaat u op de  
22 gebruikelijke manier de schildwachtklierprocedure.  
23  
24

## 25 **8. Wanneer stopt het onderzoek?** 26

27 De onderzoeker laat het aan u weten als er nieuwe informatie over het onderzoek is die  
28 belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.  
29

30 In deze situaties stopt voor u het onderzoek:  
31

- 32 • De operatie is klaar en u heeft de vragenlijst ingevuld.  
33
- 34 • U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij  
35 de onderzoeker en uw arts. U hoeft er niet bij te vertellen waarom u stopt. Als u op het moment  
36 van stoppen de schildwachtklierprocedure nog moet ondergaan, krijgt u de gewone  
37 schildwachtklierprocedure voor baarmoederhalskanker. De nieuwe techniek wordt dan niet  
38 gebruikt.
- 39 • De onderzoeker vindt het veiliger voor u om te stoppen.  
40
- 41 • Een van de volgende instanties besluit dat het onderzoek moet stoppen:
  - 42 o het UMC Utrecht,  
43 o de overheid, of  
44 o de medisch-ethische commissie die het onderzoek beoordeelt.  
45

### 46 *Wat gebeurt er als u stopt met het onderzoek?* 47

48 De onderzoekers gebruiken de gegevens die tot het moment van stoppen zijn  
49 verzameld.  
50

51 Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.  
52

## 53 **9. Wat gebeurt er na het onderzoek?** 54

### 55 *Krijgt u de resultaten van het onderzoek?* 56

57 Na de operatie kan uw arts u vertellen hoe de vergelijking van beide technieken is gegaan. Als  
58 het hele onderzoek is afgelopen, laat de onderzoeker u weten wat de belangrijkste uitkomsten  
59 zijn van het onderzoek. Wilt u dit niet weten? Zeg dat dan tegen uw arts of de onderzoeker.  
60 Hij/zij zal het u dan niet vertellen.

## 10. Wat doen we met uw gegevens?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?

We bewaren deze gegevens:

- uw naam;
- uw geboortedatum;
- uw e-mailadres;
- gegevens over uw gezondheid;
- (medische) gegevens die we tijdens het onderzoek verzamelen.

Waarom verzamelen, gebruiken en bewaren we uw gegevens?

We verzamelen, gebruiken en bewaren uw gegevens om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten openbaar te kunnen maken.

Hoe beschermen we uw privacy?

Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het ziekenhuis. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en openbare artikelen over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?

Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- Leden van de commissie die de veiligheid van het onderzoek in de gaten houdt;
- Een controleur die voor het UMC Utrecht werkt;
- Nationale en internationale toezichthoudende autoriteiten. Bijvoorbeeld de Inspectie Gezondheidszorg en Jeugd.

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens?

We bewaren uw gegevens 25 jaar in het ziekenhuis.

Mogen we uw gegevens gebruiken voor ander onderzoek?

Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander wetenschappelijk onderzoek op het gebied van baarmoederhalskanker. Daarvoor zullen uw gegevens 25 jaar worden bewaard in het ziekenhuis. In het toestemmingformulier geeft u aan of u dit goed vindt. Geeft u geen toestemming? Dan kunt u nog steeds meedoen met dit onderzoek. U krijgt dezelfde zorg.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?

U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Dit geldt voor het gebruik in dit onderzoek en voor het gebruik in ander onderzoek. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

1  
2      *Wilt u meer weten over uw privacy?*

- 3  
4      • Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op  
5      [www.autoriteitpersoonsgegevens.nl](http://www.autoriteitpersoonsgegevens.nl).  
6  
7      • Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw  
8      persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de  
9      verwerking van uw persoonsgegevens. Voor dit onderzoek is dat:  
10  
11      o      UMC Utrecht. Zie **bijlage A** voor contactgegevens en website.  
12

- 13      • Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om  
14      deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris  
15      Gegevensbescherming van uw instelling gaan. Zie **bijlage A** voor de contactgegevens. Of u  
16      dient een klacht in bij de Autoriteit Persoonsgegevens.

17      *Waar vindt u meer informatie over het onderzoek?*  
18

19      Op de volgende website(s) vindt u meer informatie over het onderzoek: [www.trialregister.nl](http://www.trialregister.nl).  
20      Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek  
21      tonen. U vindt het onderzoek door te zoeken op 'FluoreSENT study' (nummer: NL9011).  
22

## 23      **11. Krijgt u een vergoeding als u meedoet aan het onderzoek?**

24      De nieuwe techniek die wordt gebruikt in het onderzoek kost u niets. U krijgt ook geen  
25      vergoeding als u meedoet aan dit onderzoek.  
26

## 27      **12. Bent u verzekerd tijdens het onderzoek?**

28      Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. Dit is wettelijk  
29      verplicht. De verzekering betaalt voor schade door het onderzoek. Maar niet voor alle schade.  
30      In **bijlage B** vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook  
31      aan wie u schade kunt melden.  
32

## 33      **13. We informeren uw huisarts**

34      De onderzoeker stuurt uw huisarts een brief om te laten weten dat u meedoet aan het  
35      onderzoek. Dit is voor uw eigen veiligheid. Als het nodig is kunnen we contact opnemen met  
36      uw huisarts, bijvoorbeeld over uw medische geschiedenis of over de medicijnen die u gebruikt.  
37

## 38      **14. Heeft u vragen?**

39      Vragen over het onderzoek kunt u stellen aan de onderzoeker. Wilt u advies van iemand die  
40      er geen belang bij heeft? Neem dan contact op met de onafhankelijk arts dhr. Ruurda. Hij  
41      weet veel over het onderzoek maar werkt niet mee aan het onderzoek. Heeft u een klacht?  
42      Bespreek dit dan met de onderzoeker of uw eigen arts. Wilt u dit liever niet? Ga dan naar de  
43      klachtencommissie van uw ziekenhuis. In **bijlage A** staat waar u die kunt vinden.  
44

## 45      **15. Hoe geeft u toestemming voor het onderzoek?**

46      U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de  
47      informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het  
48      toestemmingsformulier in dat u achteraan deze informatiebrief vindt. U en de onderzoeker  
49      krijgen allebei een getekende versie van deze toestemmingsverklaring.  
50

51      Dank voor uw aandacht. We zijn dankbaar dat u wil nadenken over meedoen met dit  
52      onderzoek.  
53

54      Namens het FluoreSENT onderzoeksteam  
55

56      Kees Gerestein, gynaecologisch oncoloog  
57

**16. Bijlagen bij deze informatie**

- 7 A. Contactgegevens UMC Utrecht
- 8 B. Toestemmingsformulier(en)
- 9 C. Informatie over de verzekering

For peer review only



## Bijlage A: contactgegevens voor het UMC Utrecht

### Contactpersoon onderzoek:

Drs. Ilse Baeten, arts-onderzoeker

Postbus 85500

3508 GA Utrecht

Telefoonnummer 088 75 530 68

E-mail [i.g.t.baeten@umcutrecht.nl](mailto:i.g.t.baeten@umcutrecht.nl)

Bereikbaar van maandag t/m vrijdag

### Hoofdonderzoeker:

Dr. Kees Gerestein, gynaecologisch oncoloog

Postbus 85500

3508 GA Utrecht

Telefoonnummer 088 75 564 27

Email [c.g.gerestein-2@umcutrecht.nl](mailto:c.g.gerestein-2@umcutrecht.nl)

### Onafhankelijk arts:

Prof. dr. Jelle Ruurda, chirurg

Postbus 85500

3508 GA Utrecht

Telefoonnummer 088 75 580 74

Email [j.p.ruurda@umcutrecht.nl](mailto:j.p.ruurda@umcutrecht.nl)

### Klachten:

Klachtenbemiddeling UMC Utrecht

Huispost D01.343

Antwoordnummer 8419

Postbus 85500

3508 GA UTRECHT

Telefoonnummer 088 75 562 08

[www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klacht-indienen](http://www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klacht-indienen)

### Functionaris voor de Gegevensbescherming van de instelling:

UMC Utrecht t.a.v. Functionaris gegevensbescherming

Huispost Fac. 10.12

Postbus 85500

3508GA Utrecht

Email [privacy@umcutrecht.nl](mailto:privacy@umcutrecht.nl)

<https://www.umcutrecht.nl/nl/Over-Ons/Privacy>



## Bijlage B: toestemmingsformulier deelnemer aan deze studie

Behorende bij: **Een nieuwe techniek voor het opsporen van schildwachtklieren**

Met als officiële titel: De bilaterale schildwachtklier detectie van fluorescent indocyanine groen in vergelijking met technetium-99m en blauw in de schildwachtklierprocedure in stadium I-IIA cervixcarcinoom: de FluoreSENT studie

Lees dit formulier rustig door. Bij tekenen van het formulier bent u het eens met de onderstaande punten:

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts te laten weten dat ik meedoet aan dit onderzoek.
- Ik geef de onderzoekers toestemming om mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.

- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja <input type="checkbox"/>	Nee <input type="checkbox"/>
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja <input type="checkbox"/>	Nee <input type="checkbox"/>

- Ik wil meedoen aan dit onderzoek.

Mijn naam is (deelnemer): .....

Handtekening: .....

Datum : \_\_ / \_\_ / \_\_

-----  
Ik verklaar dat ik deze deelnemer volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die de toestemming van de deelnemer kan beïnvloeden? Dan laat ik dit op tijd weten aan deze deelnemer.

Naam onderzoeker (of diens vertegenwoordiger):.....

Handtekening:.....

Datum: \_\_ / \_\_ / \_\_

De deelnemer aan deze studie krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.



## Bijlage C: informatie over de verzekering

Het UMC Utrecht heeft een verzekering afgesloten voor iedereen die meedoet aan het onderzoek. De verzekering betaalt de schade die u heeft doordat u aan het onderzoek meedeed. Het gaat om schade die u krijgt tijdens het onderzoek, of binnen 4 jaar na het onderzoek. U moet schade binnen 4 jaar melden bij de verzekeraar.

Heeft u schade door het onderzoek? Meld dit dan telefonisch of per post bij deze verzekeraar:

De verzekeraar van het onderzoek is:

Naam: CNA Insurance Company Ltd

Adres: Strawinskylaan 703, 1077 XX, Amsterdam, Nederland

Telefoonnummer: +31 (0)20 57 37 274

Polisnummer: 10201366

Contactpersoon: Mw. Esther van Herk

De verzekering betaalt maximaal € 650.000 per persoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.

Let op: de verzekering dekt de volgende schade niet:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat u aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van uw kinderen of kleinkinderen.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (<https://wetten.overheid.nl>).

# BMJ Open

**Fluorescent indocyanine green versus technetium-99m and blue dye for bilateral SENTinel lymph node detection in stage I-IIA cervical cancer (FluoreSENT): protocol for a non-inferiority study**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061829.R2
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Complete List of Authors:	Baeten, Ilse; UMC Utrecht, Department of Gynaecologic Oncology Hoogendam, Jacob; UMC Utrecht, Department of Gynaecologic Oncology Braat, Arthur; UMC Utrecht, Department of Radiology and Nuclear Medicine Veldhuis, Wouter; UMC Utrecht, Department of Radiology and Nuclear Medicine Jonges, Trudy; UMC Utrecht, Department of Pathology, Division of Laboratory, Pharmacy and Biomedical Genetics Jürgenliemk-Schulz, Ina; UMC Utrecht, Department of Radiotherapy Zweemer, Ronald; UMC Utrecht, Department of Gynaecologic Oncology Gerestein, Cornelis; UMC Utrecht, Department of Gynaecologic Oncology
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3     **Title**

4     Fluorescent indocyanine green versus technetium-99m and blue dye for bilateral SENTinel lymph node  
5     detection in stage I-IIA cervical cancer (FluoreSENT): protocol for a non-inferiority study

16     **Authors:**

17     Ilse G.T. Baeten<sup>a</sup> MD, Jacob P. Hoogendam<sup>a</sup> MD PhD, Arthur J.A.T. Braat<sup>b</sup> MD PhD, Wouter B. Veldhuis<sup>b</sup>  
18     MD PhD, Geertruida N. Jonges<sup>c</sup> MD PhD, Ina M. Jürgenliemk-Schulz<sup>d</sup> MD PhD, Ronald P. Zweemer<sup>a</sup> MD  
19     PhD, Cornelis G. Gerestein<sup>a</sup> MD PhD

20     <sup>a</sup> Department of Gynaecologic Oncology, Division of Imaging and Oncology, University Medical Center Utrecht,  
21     Utrecht University, Utrecht, the Netherlands

22     <sup>b</sup> Department of Radiology and Nuclear Medicine, Division of Imaging and Oncology, University Medical Center  
23     Utrecht, Utrecht University, Utrecht, the Netherlands

24     <sup>c</sup> Department of Pathology, Division of Laboratory, Pharmacy and Biomedical Genetics, University Medical Center  
25     Utrecht, Utrecht University, Utrecht, the Netherlands

26     <sup>d</sup> Department of Radiotherapy, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht  
27     University, Utrecht, the Netherlands

28     **Corresponding author:** Ilse G.T. Baeten MD, Department of Gynaecological Oncology, Division of  
29     Imaging and Oncology, University Medical Center Utrecht, F05.126, PO Box 85500, 3508 GA Utrecht, the  
30     Netherlands. Telephone number +31 88 75 530 68. Email [i.g.t.baeten@umcutrecht.nl](mailto:i.g.t.baeten@umcutrecht.nl).

31     **Word count (excluding abstract and references):** 4296

## 27 Abstract

### 28 Introduction

29 Nowadays, two predominant methods for detecting sentinel lymph nodes (SLNs) in cervical cancer are  
30 in use. The most conventional method is a combination of a radiotracer, technetium-99m ( $^{99m}\text{Tc}$ ), and  
31 blue dye. More recently another method for SLN mapping using indocyanine green (ICG) is becoming  
32 widely accepted. ICG is a fluorescent dye, visualised intraoperatively with near-infrared (NIR)  
33 fluorescence imaging, providing real-time visual navigation. The presumed advantages of ICG over  $^{99m}\text{Tc}$ ,  
34 i.e. cheaper, nonradioactive and logically more attractive, are only valuable if its detection rate proves  
35 to be at least non-inferior. Before omitting the well-functioning and evidence based combined approach  
36 of  $^{99m}\text{Tc}$  and blue dye, we aim to provide prospective evidence on the non-inferiority of ICG with NIR  
37 fluorescence imaging.

### 38 Methods and analysis

39 We initiated a prospective non-inferiority study with a paired comparison of both SLN methods in a  
40 single sample of 101 patients with FIGO stage IA–IB2 or IIA1 cervical cancer receiving primary surgical  
41 treatment. All patients undergo SLN mapping with ICG and NIR fluorescence imaging in adjunct to  
42 mapping with  $^{99m}\text{Tc}$  (including SPECT/CT) and blue dye. Surgeons start SLN detection with ICG while  
43 being blinded for the preoperative outcome of SPECT/CT to avoid biased detection with ICG. Primary  
44 endpoint of this study is bilateral SLN detection rate of both methods (i.e. detection of at least one SLN  
45 in each hemipelvis). Since we compare strategies for SLN mapping that are already applied in current  
46 daily practice for different types of cancer, no additional risks or burdens are expected from these study  
47 procedures.

### 48 Ethics and dissemination

49 The current study is approved by the Medical Ethics Research Committee (MREC) Utrecht (reference  
50 number 21-014). Findings arising from this study will be disseminated in peer-reviewed journals,  
51 academic conferences and through patient organisations.

52 **Trial registration number:** Netherlands Trial Register NL9011; EudraCT 2020-005134-15.

## Article Summary

### Strengths and limitations of this study

- We perform a powered, prospective non-inferiority trial comparing the bilateral sentinel node detection with ICG versus the combination of radiotracer (including preoperative imaging) and blue dye in cervical cancer.
- The FluoreSENT study is designed for intrapatient endpoint comparison, which increases statistical power and – contrary to a randomised controlled trial – allows for a direct comparison of detection rate and sentinel lymph node anatomical localisation of the different tracers.
- In the presented design, surgeons are blinded for the outcome of the radiotracer when starting sentinel lymph node detection with ICG.
- A limitation of this study design is the lack of blinding for the outcome of blue dye, which is visible with the naked eye.

### Introduction

Lymph node status is the strongest prognostic factor of survival in cervical cancer patients and influences therapeutic management(1), highlighting the importance of nodal assessment. To assess nodal stage accurately and efficiently in early-stage cervical cancer patients, sentinel lymph node (SLN) mapping has emerged and could play a fundamental role in reducing the need for full pelvic lymphadenectomy. International studies are underway to assess the performance of SLN resection alone versus pelvic lymphadenectomy in cervical cancer treatment.(2, 3) For SLN mapping to be considered reliable, adequate detection and resection is essential. Since the cervix is a midline organ and lymphatic drainage is conducted bilaterally, high bilateral detection rates (defined as the proportion of patients with at least one SLN detected in each hemipelvis) are crucial for reliable SLN mapping.(4)

For mapping the SLNs, the conventional combined approach of radiotracer technetium-99m nanocolloid ( $^{99m}\text{Tc}$ ) and blue dye previously has proven to yield superior bilateral detection rates compared to using one of these tracers alone.(4-9) The radiotracer  $^{99m}\text{Tc}$  enables preoperative imaging with SPECT/CT while blue dye is added during surgery to visualize lymph nodes and afferent lymphatic vessels. However, certain disadvantages exist. Use of  $^{99m}\text{Tc}$  with SPECT/CT exposes patients to ionizing radiation. Intraoperatively, use of  $^{99m}\text{Tc}$  only gives acoustic feedback and, with conventional gamma probes, is unable to provide real-time visual guidance. The 'long' radiotracer protocol (i.e. one day preoperative admission for SPECT/CT) can be logistically challenging (demanding a nuclear medicine unit with safety protocols for handling), time consuming, involving longer hospital stay, and leading to higher patient burden. Also,  $^{99m}\text{Tc}$  usage is costly, especially in combination with preoperative SPECT/CT. Although the combination with intraoperative use of blue dye is beneficial in terms of bilateral detection rate, in a

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3     92 subset of patients blue dye is associated with allergic reactions, that may be severe (around 0.6%).(9, 10)  
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5     93 Common adverse effects related to blue dye are localized swelling or pruritus (2-4%), transient  
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7     94 discolouration of skin and urine (>95%) and a decrease in pulse oximetry readings due to colorimetric  
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9     95 interference.(11, 12)

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11     96 The aforementioned disadvantages contributed to the recent shift towards SLN mapping with  
12     97 indocyanine green (ICG).(13) ICG is a nonradioactive fluorescent dye that is visualised intraoperatively  
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14     98 with near-infrared (NIR) fluorescence imaging, providing real-time visual navigation. Recently, the FDA  
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16     99 approved ICG for the indication of lymphatic mapping in uterine and cervical cancers.(14) Compared to  
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18     100  $^{99m}\text{Tc}$ , ICG is non-radioactive, cheaper and logically more attractive. Compared to blue dye, ICG has a  
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20     101 better tissue penetration and a lower allergy risk. Overall, the use of ICG may lead to less burden on the  
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22     102 patient as its use enables shorter hospital admissions and injection under anaesthesia. (15-17) The  
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24     103 feasibility of ICG has been demonstrated and early reports showed ICG yields high SLN detection rates  
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26     104 in patients with early-stage cervical cancer.(18-21) Limitations of ICG include costs of NIR fluorescence  
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28     105 equipment and less guidance towards unexpected SLN positions because of the absence of preoperative  
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30     106 imaging.(22) Research in prostate cancer therefore suggests that preoperative SLN mapping provided  
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32     107 by SPECT/CT remains essential in guiding intraoperative SLN localisation.(23) Another pitfall is the tissue  
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34     108 penetration of NIR fluorescence imaging of approximately 1 cm, meaning it can be detected through a  
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36     109 centimetre of overlying tissue,(24) which is especially limiting in patients with a high body mass index.(25,  
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38     110 26) Also, the small hydrodynamic diameter of the ICG molecule may result in rapid spreading towards  
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40     111 second and third echelon nodes,(16) undesirably leading to higher number of removed (false) SLNs.  
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42     112 Although clinically the shift towards ICG seems to be in progress, shifting to an easy-to-use technique  
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44     113 is not justified without prior evidence of its clinical reliability and validity wherein it performs at least as  
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46     114 good as the current standard of care.

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48     115 In both endometrial and cervical cancer adequately powered prospective trials comparing ICG with the  
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50     116 more conventional method of  $^{99m}\text{Tc}$  and blue dye are lacking.(27-30) The surgical practice has changed  
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52     117 rapidly towards ICG in absence of level A evidence on its diagnostic accuracy. The unexpected recent  
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54     118 findings of the LACC trial have again stressed the importance of compelling evidence before switching  
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56     119 to a new surgical technique.(31) Regarding cervical cancer, a prospective study by Lührs et al. compared  
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58     120 ICG with intraoperatively administered  $^{99m}\text{Tc}$  in 65 cervical cancer patients, without adding blue dye and  
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60     121 without performing preoperative SPECT/CT imaging. The researchers reported a significant higher  
   bilateral detection rate of ICG compared to  $^{99m}\text{Tc}$  without any significant improvement by combining the  
   two. The lack of preoperative imaging in this study possibly affected the bilateral detection rate of  $^{99m}\text{Tc}$   
   negatively, which was low at 60%.(32) The FILM trial, a randomised non-inferiority trial comparing ICG  
   with blue dye for SLN mapping in predominantly endometrial cancer (n=169; 96%) though also cervical

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3 126 cancer (n=7; 4%), reported significantly higher SLN detection rates with ICG than with blue dye only.(30)  
4 127 Besides its limited applicability in cervical cancer, a second major limitation is the absence of a  
5 128 radiotracer, making a comparison between ICG and the conventional combined approach impossible.  
6 129 Regarding endometrial cancer, prospective studies on the accuracy of ICG report greatly varying bilateral  
7 130 detection rates, ranging from 52% to 82%.(27-29, 33, 34) Researchers of the FIRES and SENTOR trial  
8 131 report a bilateral detection rate of ICG (52 and 78%, respectively) that is lower than the reported bilateral  
9 132 detection rate of  $^{99m}\text{Tc}$  with blue dye in relatively large prospective studies (e.g. 80.5% in the SENTICOL  
10 133 study(7)).(27, 29) Soliman et al. prospectively studied the bilateral detection rate in endometrial cancer  
11 134 patients injected with either ICG, blue dye or  $^{99m}\text{Tc}$  with blue dye.(33) Interestingly, the bilateral detection  
12 135 rate appeared to be highest with  $^{99m}\text{Tc}$  with blue dye (82% versus 52% with ICG only). However, as stated  
13 136 by the authors, the study was not powered to detect a difference in detection rates between the methods  
14 137 ( $p=0.35$ ). How et al. compared the three tracers (blue dye, ICG and  $^{99m}\text{Tc}$ ) simultaneously in 100 patients  
15 138 with endometrial cancer undergoing SLN mapping.(34) They found no significant difference in the  
16 139 bilateral detection of ICG versus  $^{99m}\text{Tc}$  (65% with ICG vs 71% with  $^{99m}\text{Tc}$ ,  $p=0.36$ ). When they compared  
17 140 ICG to the combination of  $^{99m}\text{Tc}$  and blue dye, the difference in bilateral detection rate increased in  
18 141 favour of the conventional method: 65% with ICG versus 75% with  $^{99m}\text{Tc}$  with blue dye. Of note, their  
19 142 results showed that  $^{99m}\text{Tc}$  was the only tracer that detected all metastatic SLNs, which substantiates that  
20 143 a reliable SLN procedure can impact the survival.

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34 144 Retrospective cohort studies reporting on the comparison of ICG versus  $^{99m}\text{Tc}$  combined with blue dye  
35 145 exist, but are generally of insufficient quality, underpowered and potentially suffer from publication bias.  
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37 146 After a systematic review and meta-analysis of the available literature comparing ICG with  $^{99m}\text{Tc}$  and blue  
38 147 dye, we found that the pooled bilateral detection rate with ICG appeared to be significantly higher.(35)  
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40 148 However, in adherence with the Grading of Recommendations, Assessment, Development, and  
41 149 Evaluation (GRADE) guidelines, the quality of evidence was too low to provide strong recommendations  
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43 150 and directly omit the combined approach of a radiotracer and blue dye. In addition, all included studies  
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45 151 reported a higher average number of identified SLNs when using ICG as a tracer, indicating these are  
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47 152 not likely to be all SLNs but rather second echelon lymph nodes. Failing to excise the true SLN could  
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49 153 result in missed lymph node metastases. Currently, in both systematic reviews and European guidelines  
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51 154 on cervical cancer, no consensus on the use of tracer has been reached and both methods of sentinel  
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53 155 lymph node detection are approved.(35-37) Before omitting any well-functioning and evidence based  
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55 156 procedure ( $^{99m}\text{Tc}$  combined with blue dye) high quality evidence on the performance of ICG in cervical  
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57 157 cancer SLN mapping is needed. In the FILM trial by Frumovitz et al. it was stated: "*Although the*  
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59 158 *combination of blue dye and radiocolloid might be better than blue dye alone and equivalent to*  
60 159 *indocyanine green in detecting sentinel nodes, no studies – either prospective or retrospective – have*

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3 160 compared the combination of blue dye and radiocolloid with indocyanine green.". (30) With our study, we  
4 intend to perform the proposed prospective study comparing ICG with the combination of radiotracer  
5 and blue dye (including preoperative SPECT/CT) in early-stage cervical cancer patients. The presumed  
6 benefits of ICG are only valuable if its detection rate proves to be at least non-inferior to  $^{99m}\text{Tc}$  and blue  
7 dye.  
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12 165 **Methods and analysis**  
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16 167 **Study design**  
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18 168 The FluoreSENT study is initially designed as a prospective, multicentre, non-randomised, single-arm,  
19 cross-sectional study in which we compare two SLN methods in early-stage cervical cancer patients  
20 undergoing primary surgical treatment (FIGO stage IA – IB2 or IIA1): ICG with NIR fluorescence imaging  
21 versus  $^{99m}\text{Tc}$  (including preoperative SPECT/CT) and blue dye. The study started in July 2021 and is  
22 coordinated by the University Medical Center Utrecht (UMCU) and monocentric in the rollout phase. We  
23 plan to expand this study in other Dutch tertiary referral centres to increase the accrual rate. The planned  
24 end date of this study is July 2024.  
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31 176 Given that the current bilateral detection rate using  $^{99m}\text{Tc}$  combined with blue dye is already high (86%  
32 in own cohort) and the use of ICG has substantial benefits, a non-inferiority design is justified.(38) When  
33 non-inferiority is reached, a switch in standard care to ICG with NIR fluorescence imaging (i.e.  
34 abandoning  $^{99m}\text{Tc}$  and blue dye) is supported, which will reduce the physical burden on the patient and  
35 logistic and financial burden on the health care system. If the detection rate with ICG proves to be inferior  
36 to  $^{99m}\text{Tc}$  with blue dye, the extra burden of the conventional method would be justified as, in the end,  
37 patients will benefit most from the highest achievable bilateral detection rate. It is important to note  
38 that this is not an equivalence trial. When SLN mapping with ICG produces a higher bilateral detection  
39 rate than SLN mapping with  $^{99m}\text{Tc}$  and blue dye, this is not considered a negative study result, whereas  
40 this is clearly a convincing reason to change the current practice. We chose bilateral detection rate as  
41 the primary endpoint because bilateral detection of SLNs has proven to decrease false negative rate and  
42 is thus considered to improve reliability and oncological safety.(4, 39) This protocol has been developed  
43 in line with research protocol template of the Central Committee on Research Involving Human Subjects  
44 (CCMO) and the SPIRIT recommendations.(40)  
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48 191 **Study population**  
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50 192 The subjects will be drawn from a population of patients with histopathologically proven primary  
51 malignancy of the cervix uteri. Patients are eligible to participate if they are planned for a (robot-assisted)

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3 194 laparoscopic or open SLN procedure as part of the standard surgical treatment for FIGO stage IA1-IB2  
4 195 or IIA cervical cancer (according to the FIGO 2018 guidelines(41)), aged ≥18 years and able to provide  
5 196 informed consent. Exclusion criteria are: pregnancy or current breastfeeding, renal insufficiency stage 3  
6 197 or 4, prior allergic reaction to ICG, <sup>99m</sup>Tc or patent blue, prior severe allergic reaction to iodine. Informed  
7 198 consent will be obtained before the start of any study activity.  
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13 200 **Sample size**  
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15 201 The sample size calculation was based on our own data and current literature. Data from our historical  
16 202 cohort showed a bilateral detection proportion of 86% (95% CI 80-91%) for SLN mapping with <sup>99m</sup>Tc and  
17 203 blue dye (manuscript in preparation; (38)). The pooled proportion of bilateral detection rate of ICG was  
18 204 found to be between 89.4% and 91.5%, depending on how studies in the meta-analysis were handled  
19 205 (in preliminary analysis). Based on consensus discussion by clinicians in the study team and a  
20 206 comprehensive review of the literature, a non-inferiority margin of 0.05 was set. For assessing non-  
21 207 inferiority in paired proportions the asymptotic test statistic, which is the so-called Nam score test,  
22 208 or restricted maximum likelihood estimation (RMLE-based) test statistic was used.(42) The power and  
23 209 sample size was calculated in the statistical software package PASS (Power Analysis and Sample Size),  
24 210 verified for non-inferiority tests (one-sided) for two correlated proportions.(43) The calculations were  
25 211 checked by a statistician (power formula is provided in the PASS User's Guide(43)).  
26  
27 212 In conclusion, comparing a proportion (<sup>99m</sup>Tc and blue dye at 0.86, ICG 0.89) in one sample with a non-  
28 213 inferiority margin of 0.05, with a Type I error ( $\alpha$ ) set at 0.05, Type II error ( $\beta$ ) set at 0.2 (power  $1-\beta= 0.8$ ),  
29 214 and Nuisance set at 0.12 (based on the proportion of discordant pairs), we require a sample size of 101  
30 215 cases. The complete list of parameters used for the power calculation is provided in Appendix 1.  
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33 216 **Investigational product**  
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35 217 ICG is a fluorescent agent used for diagnostic purposes in adults and children with a benign safety  
36 218 profile. One of the diagnostic purposes is fluorescence imaging of lymph nodes and delineation of  
37 219 lymphatic vessels in the cervix and uterus in patients with solid tumours during lymphatic mapping. No  
38 220 therapeutic effects are expected. ICG (VERDYE 25mg, Diagnostic Green GmbH, Germany) is registered  
39 221 for diagnostic purposes in adults under Dutch RVG number 31052.  
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42 222 Allergic reactions and anaphylactic shocks due to ICG were reported in very rare (<0.01%) cases. In  
43 223 patients with renal insufficiency, the risk of anaphylactic shock appears to be higher. In very rare cases  
44 224 spasms of the coronary arteries are described. Radioactive iodine uptake studies should not be  
45 225 performed for at least a week following the use of ICG. No other complications or potential risks of ICG  
46 226 are reported.(14)  
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**227 Trial intervention**

228 The flowchart in **Figure 1** presents a schematic overview of the study design. All subjects undergo a SLN  
229 procedure as part of the surgical treatment and receive ICG injection in adjunct to the current combined  
230 approach. Subjects will be preoperatively injected with  $^{99m}\text{Tc}$  followed by a SPECT/CT 90-120 minutes  
231 post-injection (according to current standard-of-care).(38) The surgeon (gynaecological oncologist) will  
232 not consult the SPECT/CT preoperatively (secured by automated logging of consultation). At the start of  
233 surgery, subjects are injected with four millilitres of ICG 1.25 mg/ml (study procedure) and four millilitres  
234 of blue dye (standard-of-care) under general anaesthesia; 1 ml of both tracers into each quadrant of the  
235 cervix (i.e. at 3, 6, 9 and 12 o'clock, following the internal protocol). During surgery the SLNs will be first  
236 identified with NIR fluorescence light using FireFly fluorescent imaging system (Intuitive Surgical Inc.) in  
237 robotic surgery or a CE marked NIR fluorescence platform applicable to laparoscopic or laparotomic  
238 surgery; in this light NIR fluorescent nodes will light up green (**Figure 2**). Localisation of each NIR  
239 fluorescent SLN will be reported. When the NIR fluorescent SLN(s) are identified, the gynaecological  
240 oncologist will check the SLN(s) for radioactivity with a gamma probe (either *in vivo* or *ex vivo*) and blue  
241 colour. When completed, the procedure is repeated in the contralateral hemipelvis. Results are reported  
242 as follows: of each SLN the localisation is reported according to a standardised format (see Appendix 2)  
243 and it is stated if detected with NIR fluorescence (ICG), radioactivity ( $^{99m}\text{Tc}$ ) and/or blue colour (blue dye).  
244 All SLNs identified are excised. After finishing this procedure bilaterally, the surgeon consults the  
245 SPECT/CT (time of deblinding is logged both automatically and manually) and reports whether  
246 radioactive node(s) on SPECT/CT correspond to the excised SLN(s). To prevent missing SLNs, the pelvic  
247 site will be checked for residual radioactive nodes and blue nodes, and excised, if present. Residual  
248 radioactivity of the surgical site will be measured and deemed negative if background counts are less  
249 than 10% of the maximum SLN count.

250 Blue dye and ICG are injected sequentially, before entering the retroperitoneal space. Previous studies  
251 using a combined injection of patent blue and ICG experienced no clotting of the two dyes, both at  
252 macroscopic and microscopic level.(34, 44, 45) To prevent from bias in detection of SLNs, injecting blue  
253 dye in a later stage of surgery – i.e. after SLN mapping with ICG and NIR fluorescence is completed – has  
254 been explored. However, starting SLN mapping with ICG would result in anatomical structures and  
255 lymphatic vessels that have already been destructed. Because of the destructed lymph vessels, injecting  
256 blue dye in a later stage would underestimate the true benefit as the dye will not reach the lymph nodes.  
257 This intrapatient study design is thereby limited by the inability of blinding for the outcome of blue dye.  
258 Except for injection of ICG and detection with NIR fluorescence imaging while blinded for the assessment  
259 of the SPECT/CT, the complete treatment is maintained according to the current standard-of-care.  
260 Intraoperative recordings and pictures can be made for retrospective tumour-to-background ratio

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3 261 analysis. All follow-up visits take place according to the national guidelines. There is no special follow-  
4 up required for subjects in this study. Subjects are asked to fill in the IN-PATSAT32 questionnaire  
5 postoperatively, developed by European Organisation for Research and Treatment of Cancer (EORTC),  
6 for assessing patients' perception of the quality of hospital-based care (not mandatory).  
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10 265 **Outcomes**  
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13 266 The primary outcome is bilateral detection rate of SLNs with ICG and NIR fluorescence imaging versus  
14  $^{99m}\text{Tc}$  (including pre-operative SPECT/CT) and blue dye. SLN is defined as the first lymph node(s) of each  
15 hemipelvis to receive afferent lymphatic drainage from the primary cervical tumour, identified by either  
16 ICG, gamma radiation using  $^{99m}\text{Tc}$  or blue dye. Bilateral detection is defined as number of patients  
17 detected with at least one SLN in each hemipelvis.  
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20 270  
21 271 Secondary outcomes include: (1) overall (i.e. at least unilateral) detection rate, sensitivity and false  
22 negative rate (FNR) of ICG and  $^{99m}\text{Tc}$  and blue dye, with pelvic lymph node dissection (PLND) as the  
23 reference standard to confirm tumour positive lymph nodes (part of current standard-of-care); (2)  
24 correlation between NIR fluorescent, radioactive (both intraoperative and with SPECT/CT) and blue  
25 stained SLNs in terms of anatomical location; (3) adverse events of ICG,  $^{99m}\text{Tc}$  and blue dye; (4) time to  
26 complete SLN detection with ICG versus  $^{99m}\text{Tc}$  and blue dye; (5) cost-effectiveness comparison (cost of  
27 procedure versus yielded bilateral detection rate) of ICG versus  $^{99m}\text{Tc}$  and blue dye SLN detection; (6)  
28 surgical evaluation of NIR fluorescent imaging (usability) measured with two short questionnaires  
29 tailored for the surgeons; and (7) patient satisfaction with the oncological care and procedure measured  
30 with the validated EORTC IN-PATSAT32 questionnaire.  
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34 281 The basic clinical, surgical and histopathological parameters will be recorded, including: age at diagnosis,  
35 body mass index (BMI, in kg/m<sup>2</sup>), history of abdominal surgery, ASA classification (American Society of  
36 Anaesthesiologists), FIGO stage (2018), type of procedure, tumour histology and size, lymph vascular  
37 space invasion (LVSI), nodal count and status, parametrial involvement, vaginal involvement, positive  
38 resection margins, and adjuvant or adjusted treatment (the latter due to intraoperative finding of  
39 positive lymph nodes). Subanalysis will evaluate if these parameters are possible confounders or effect  
40 modifiers.  
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44 289 **Data collection and management**  
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46 290 All measurements will be systematically recorded using an electronic Clinical Report Form (eCRF) build  
47 in Castor Electronic Data Capture (EDC) system. Data will be collected in coded form and monitored by  
48 data managers from the UMC Utrecht. Baseline characteristics are collected pseudonymously from the  
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3 293 medical records in consultation with the data management department of the research centre(s). All  
4 294 study procedures at the research centre(s) are monitored by an independent monitor during multiple  
5 295 visits according to a specified protocol.

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8 296 The principal investigators at the research centre(s) bear responsibility for safe data handling. After the  
9 297 project is finished, data will be stored for 25 years according to the current Medical Research Involving  
10 298 Human Subjects Act (WMO). Handling of personal data will comply with the EU General Data Protection  
11 299 Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.

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14 300 **Adverse events**

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17 301 Adverse events are defined as any undesirable experience occurring to a subject during the study,  
18 302 whether or not considered related to the intervention (SLN mapping with ICG and NIR fluorescence). All  
19 303 adverse events reported spontaneously by the subject or observed by the investigator or his staff will be  
20 304 recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs in the  
21 305 48 hours following the SLN procedure. The sponsor will report the SAEs through the Dutch web portal  
22 306 ToetsingOnline to the accredited MREC that approved the protocol, within 7 days of first knowledge for  
23 307 SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete  
24 308 the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after  
25 309 the sponsor has first knowledge of the serious adverse events.

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28 310 **Statistical analysis**

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31 311 We will perform a comparison (single sample) of two diagnostic modalities and aim to assess non  
32 312 inferiority (note: not equivalence) of the ICG SLN mapping in terms of bilateral detection rate. Our  
33 313 analysis is based on previous literature on non-inferiority for paired binary data.(42) Statistical software  
34 314 programs SPSS and R will be used to perform the analyses. The measured primary endpoint is the  
35 315 proportion of bilateral SLN detection which is tested in a paired setting. The null(H<sub>0</sub>) and alternative(H<sub>1</sub>)  
36 316 hypotheses for this non-inferiority study are as follows:

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44 317     • *H<sub>0</sub>*: SLN mapping with ICG is inferior to SLN mapping with <sup>99m</sup>Tc and blue dye with respect to  
45 318         the proportion of bilaterally detected sentinel nodes.  
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51 319     • *H<sub>1</sub>*: SLN mapping with ICG is non-inferior to SLN mapping with <sup>99m</sup>Tc and blue dye with respect  
52 320         to the proportion of bilaterally detected sentinel nodes.

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322 The analysis of all outcome data will be performed using intrapatient comparison (McNemars test).  
323 Categorical and continuous data will be presented in a quantitative way. The bilateral detection rates of  
324 ICG, <sup>99m</sup>Tc and blue dye are presented separately with corresponding 95% confidence intervals.  
325 Categorical data will be analysed using the Fisher Exact or Chi-square, as appropriate. For continuous

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3 326 outcomes t-test will be used in case of normally distributed data. If not normally distributed, Mann-  
4 Whitney-U test will be performed. Besides 95% confidence intervals, p-values will be reported with a  
5 value of <0.05 considered significant.  
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9 329 In case of identified inconsistencies or missing data, additional source documents will be requested from  
10 the study site to resolve ongoing inconsistencies. If necessary, patients are called to resolve missing data.  
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12 331 If missing data restrict further analysis, multiple imputation analyses will be conducted.  
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### 15 332 **Patient and public involvement**

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17 333 Members of patient organisation Stichting Olijf were involved in the design of this study.  
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### 20 334 **Ethics and dissemination**

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22 335 This current study was approved by Institutional Review Board and Medical Research Ethics Committee  
23 Utrecht (number 21-014) in accordance with the Dutch Medical Research Involving Human Subjects Act  
24 (WMO) and other applicable Dutch and European guidelines, regulations and Acts. The study was  
25 registered in the Netherlands Trial Register (number NL9011). All subjects will have to sign and date  
26 written informed consent. No study activities will occur prior to obtaining consent. Subjects retain the  
27 right to withdraw at any point for any reason. See Appendix 3 for the approved version of the Dutch  
28 patient information and informed consent form for this study (in line with the model form provided by  
29 the Central Committee on Research Involving Human Subjects).

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31 340 This study has been assessed as a low risk study. ICG is given in adjunct to the current standard of care  
32 and subjects are not withheld of any type of standard treatment. Risks associated with participation can  
33 be considered negligible. Participating in this study will be associated with minor discomfort and might  
34 be beneficial for individuals, as mapping with ICG might result in higher SLN detection rates (based on  
35 previous literature). This study intends to improve oncological care and prognosis for all early-stage  
36 cervical cancer patients.

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38 343 We will ensure our findings and the acquired knowledge will be transferred to clinicians and researchers  
39 in the field. Findings arising from this study will be published at national and international conferences.  
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41 351 The final manuscript will be submitted for publication to an open access peer-reviewed scientific journal.  
42  
43 352 Both positive and negative trial results will be disclosed. Results will also be updated in the Netherlands  
44 Trial Register, which is the primary registry for the Netherlands and recognized and accepted by the  
45 WHO and ICMJE. Subjects and cervical cancer patients will be informed about the study results by the  
46 newsletter and social media accounts of patient organisation Stichting Olijf.  
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50 357 **Author contributions**

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3 358 IGT Baeten: Conceptualization, Methodology, Writing – Original Draft, Visualization.  
4  
5 359 JP Hoogendam: Conceptualization, Methodology, Writing - Original Draft, Validation (as  
6 epidemiologist and fellow gynaecological oncology).  
7  
8 361 AJAT Braat: Methodology, Validation (as radiologist with expertise in nuclear medicine and use of  
9 technetium-99m SPECT/CT imaging), Writing - Review & Editing.  
10  
11 362 WB Veldhuis: Validation (as radiologist with expertise in gynaecologic oncology), Writing - Review &  
12  
13 364 Editing.  
14  
15 365 GN Jonges: Validation (as pathologist with expertise in pathological assessment of SLNs and cervical  
16 cancer), Writing - Review & Editing.  
17  
18 367 IM Jürgenliemk-Schulz: Validation (as radiation oncologist with expertise in cervical cancer treatment),  
19  
20 368 Writing - Review & Editing.  
21  
22 369 RP Zweemer: Conceptualization, Methodology, Validation (as gynaecological oncologist), Writing -  
23  
24 370 Review & Editing.  
25  
26 371 CG Gerestein: Conceptualization, Methodology, Validation (as gynaecological oncologist), Writing -  
27  
28 372 Review & Editing, Supervision.  
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30 373  
31 374 **Funding statement**  
32  
33 In the set-up and rollout phase this (monocentre) research received no specific grant from any funding  
34 agency in the public, commercial or not-for-profit sectors. In order to expand this study to other Dutch  
35 tertiary centres we are applying for funding within the public sector. If the application is granted, we will  
36 ensure that the funder is not going to be involved in collection, management, analysis and interpretation  
37 of data, writing of the manuscript and decision to submit the manuscript for publication, nor does it  
38 have authority over the publications.  
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43 382 **Competing interests**  
44  
45 RZ is a proctor for robot-assisted surgery in gynaecological oncology on behalf of Intuitive Surgical Inc.  
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47 All other authors declare no conflicts of interest.  
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12 555  
13 **Figure legends**  
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15 556 **Figure 1.** Flowchart of study procedures. Blue boxes represent the current standard of care; red boxes  
16 557 represent the study specific procedures.  
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18 558 **Figure 2.** Fluorescence guided surgery showing lymphatic vessels (left) and sentinel lymph node (right).  
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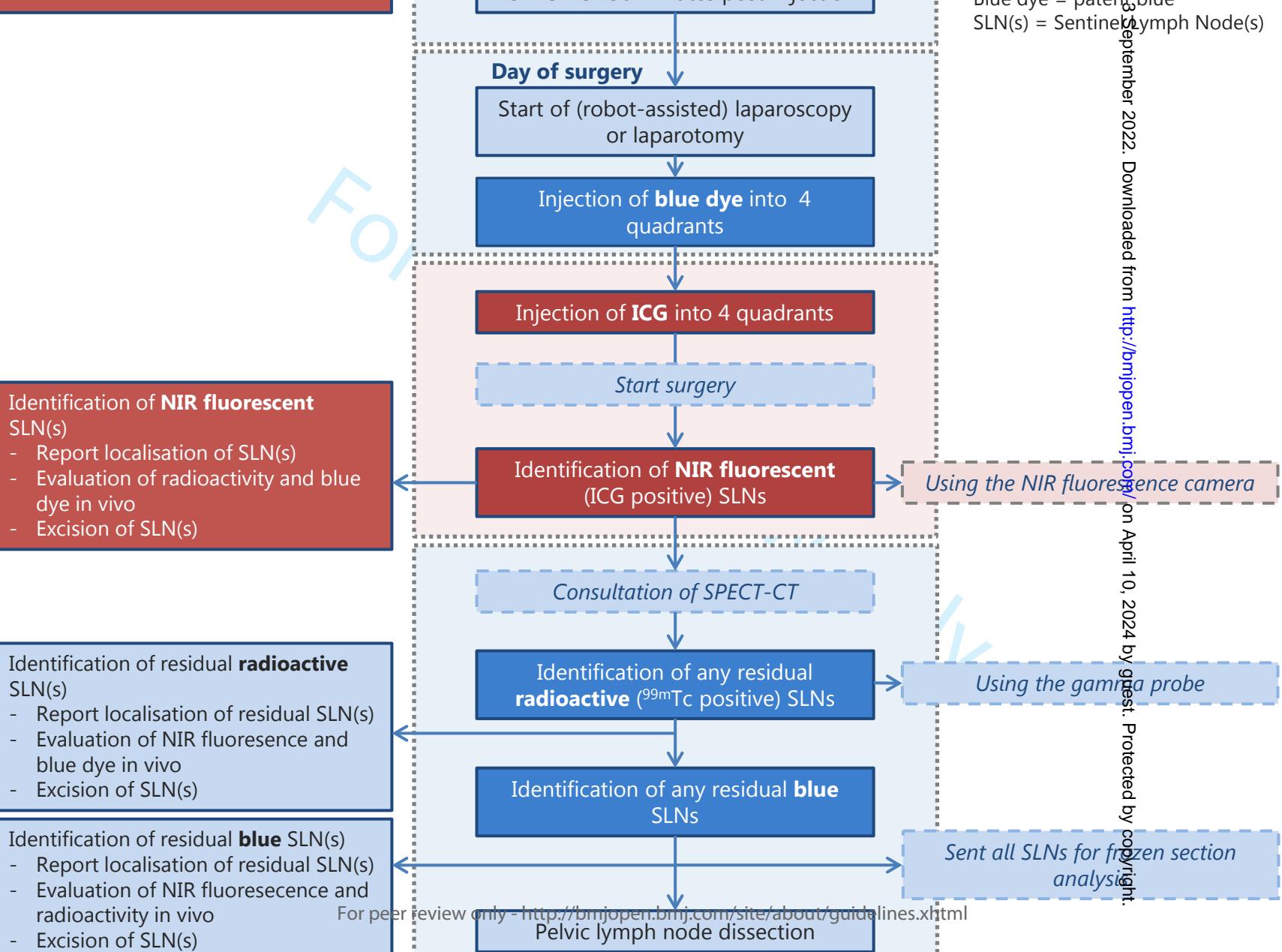
Surgeons blinded for assessment  
SPECT-CT

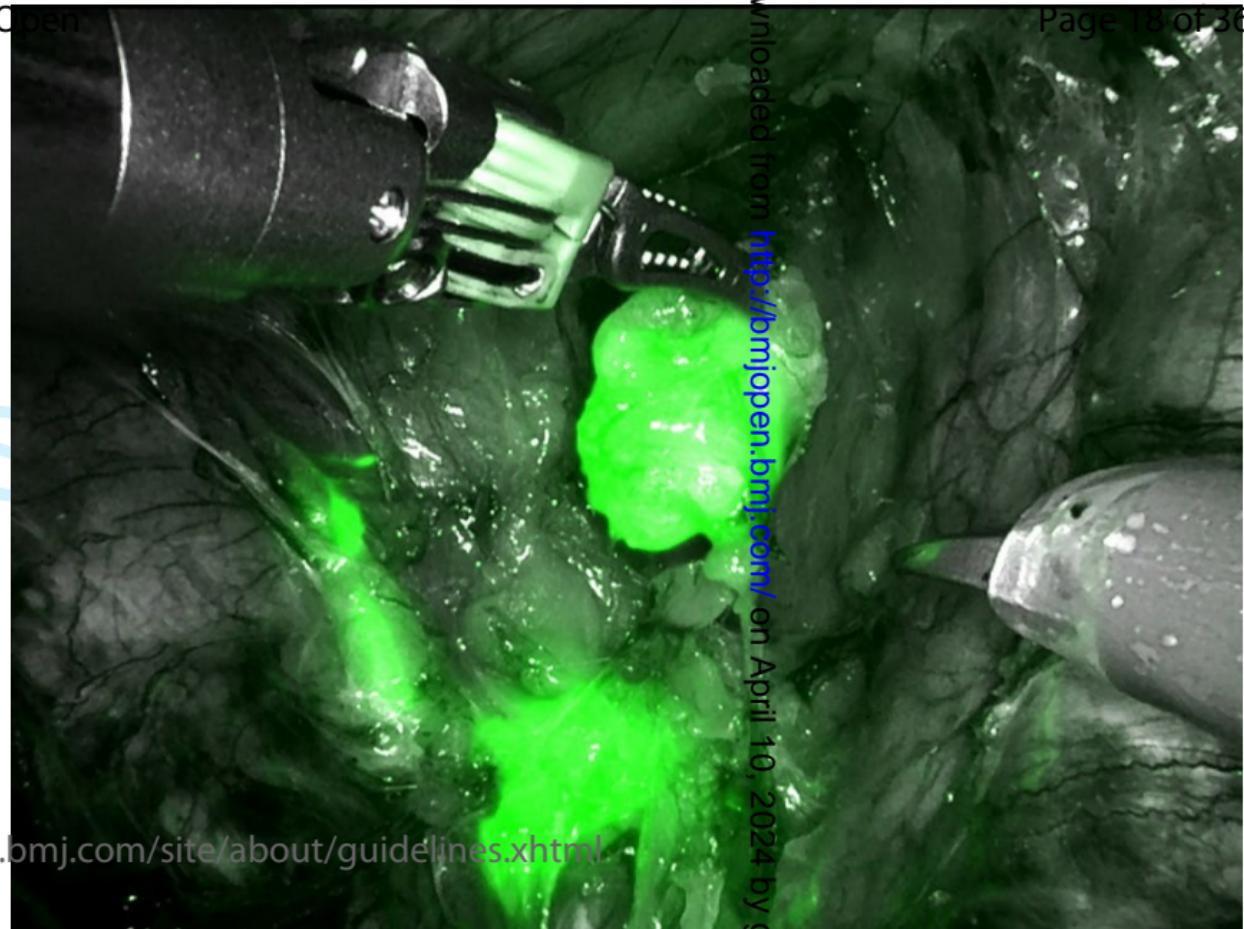
### One day preoperative BMJ Open

- Injection of  $^{99m}\text{Tc}$
- SPECT-CT 90 minutes post-injection

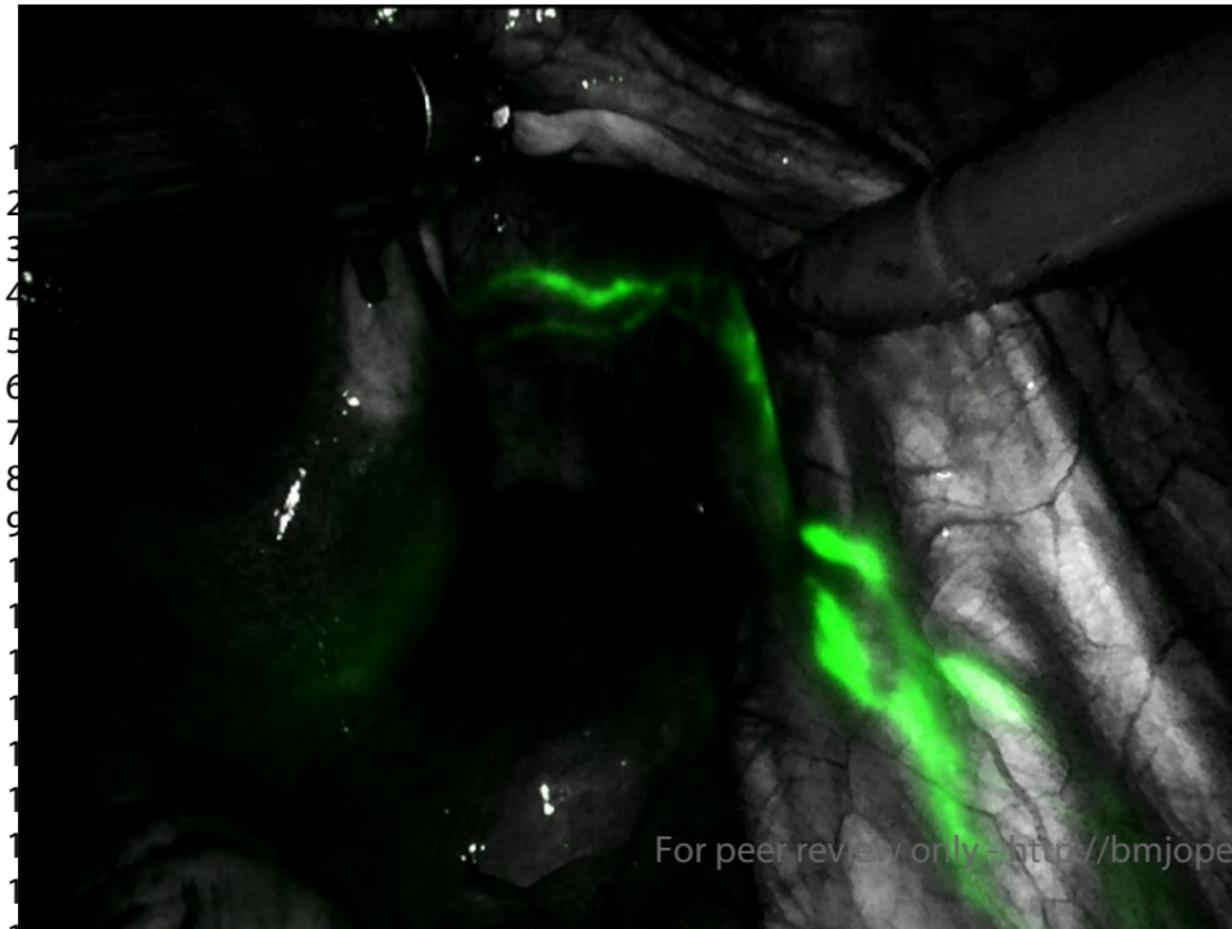
ICG = Indocyanine Green  
NIR = Near-infrared

$^{99m}\text{Tc}$  = Technetium-99m nanocolloid  
Blue dye = patent blue  
SLN(s) = Sentinel Lymph Node(s)





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## Appendix 1

### Sample size calculation

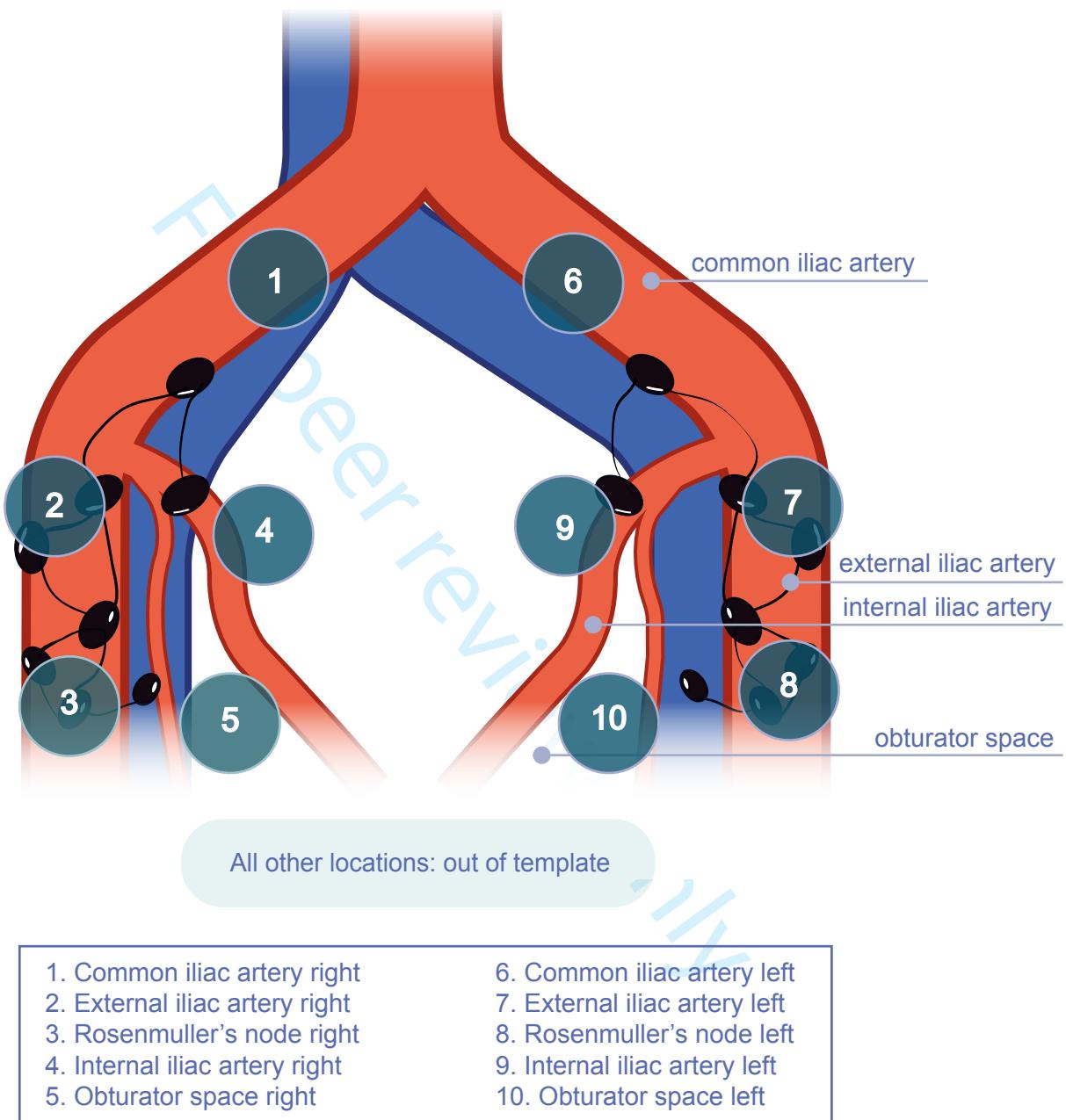
For assessing non-inferiority in paired proportions we will use an asymptotic test statistic, which is the so-called Nam score test, or restricted maximum likelihood estimation (RMLE-based) test statistic.<sup>(1)</sup> The power and sample size was calculated in the statistical software package PASS (Power Analysis and Sample Size), verified for non-inferiority tests (one-sided) for two correlated proportions.<sup>(2)</sup> The calculations were checked by a statistician (the power formula is given in the PASS User's Guide).

We set the following parameters in PASS based on consensus discussion by the clinicians in our study team and a comprehensive review of the aforementioned literature:

- *Power* is the probability of rejecting a false null hypothesis. Set at 0.80.
- *Equivalence Difference (De)* is the maximum difference between the two proportions that is still called 'equivalent.' Set at 0.05 (equal to the non-inferiority margin).
- *Actual Difference (Da)* is the actual difference between Pt and Ps. That is, Da = Pt-Ps. Set at 0.03.
- *Treatment Proportion (Pt)* is the response proportion to the treatment (experimental or new) test. Set at 0.89.
- *Standard Proportion (Ps)* is the response proportion to the standard (reference or old) test. Set at 0.86.
- The *Nuisance Parameter* is a value that is needed, but is not a direct part of the hypothesis. The parameter is based on the proportion of discordant pairs. Set at 0.12.
- *Alpha ( $\alpha$ )* is the probability of rejecting a true null hypothesis. Set at 0.05.
- *Beta ( $\beta$ )* is the probability of accepting a false null hypothesis. Set at 0.20

### References

1. Liu JP, Hsueh HM, Hsieh E, Chen JJ. Tests for equivalence or non-inferiority for paired binary data. *Stat Med*. 2002 Jan 30;21(2):231-45.
2. Hintze JL. Non-Inferiority Tests for Two Correlated Proportions. *PASS User's Guide I*. Kaysville, Utah: NCSS; 2008. p. 221-36.





# Informatie voor deelname aan medisch-wetenschappelijk onderzoek

## Een nieuwe techniek voor het opsporen van schildwachtklieren

**Officiële titel:** De bilaterale schildwachtklier detectie van fluorescent indocyanine groen in vergelijking met technetium-99m en blauw in de schildwachtklierprocedure in stadium I-IIA cervixcarcinoom: de FluoreSENT studie

### Inleiding

Beste mevrouw,

U krijgt deze brief omdat er bij u baarmoederhalskanker is gevonden. Er komt nu ongetwijfeld veel op u af. Toch hopen we dat u tijd wil maken voor het lezen van deze informatiebrief over meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig.

U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Lees de informatie rustig door. Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage C.

### Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, professor Ruurda.
- Lees de informatie op [www.rijksoverheid.nl/mensenonderzoek](http://www.rijksoverheid.nl/mensenonderzoek).

### 1. Algemene informatie

Het UMC Utrecht heeft dit onderzoek opgezet. Hieronder noemen we het UMC Utrecht steeds de 'opdrachtgever'. De onderzoekers, dit zijn artsen en onderzoeksverpleegkundigen, voeren het onderzoek uit. Voor dit onderzoek zijn in totaal 101 vrouwen met baarmoederhalskanker nodig. De medisch-ethische toetsingscommissie Utrecht heeft dit onderzoek goedgekeurd.

### 2. Wat is het doel van het onderzoek?

U krijgt binnenkort een operatie voor de behandeling van baarmoederhalskanker. De schildwachtklierprocedure is hier een onderdeel van. Dit houdt in dat de lymfeklieren die als eerste aansluiten op de tumor verwijderd worden om zeker te weten dat daar geen uitzaaiingen in zitten. Deze lymfeklieren worden ook wel schildwachtklieren genoemd. De schildwachtklieren kunnen opgespoord worden door bepaalde stoffen in te spuiten rond de tumor. Deze stoffen 'kleuren' de schildwachtklieren, zodat de arts kan zien waar de schildwachtklieren zitten. Er zijn verschillende technieken voor het 'kleuren' van de schildwachtklier beschikbaar.

In dit onderzoek bekijken we de werking van een nieuwe techniek voor het opsporen van de schildwachtklieren. We vergelijken de nieuwe techniek met de techniek die we nu gebruiken om zo te beoordelen welke de beste is.



### 3. Wat is de achtergrond van dit onderzoek?

Welke techniek gebruiken we nu voor het opsporen van schildwachtklieren?

Bij de huidige techniek sput de arts een licht radioactieve stof in rondom de tumor. Hierna krijgt u een scan. Dit gebeurt meestal al één dag voor de operatie. Tijdens de operatie sput de arts ook nog een blauwe kleurstof in. Beide stoffen maken de schildwachtklieren herkenbaar tijdens de operatie. De blauwe kleurstof kleurt soms het gezicht en meestal de urine tot enkele dagen na de operatie blauw. Ook kan de blauwe kleurstof een allergische reactie veroorzaken in iets minder dan 1 op de 100 gevallen.

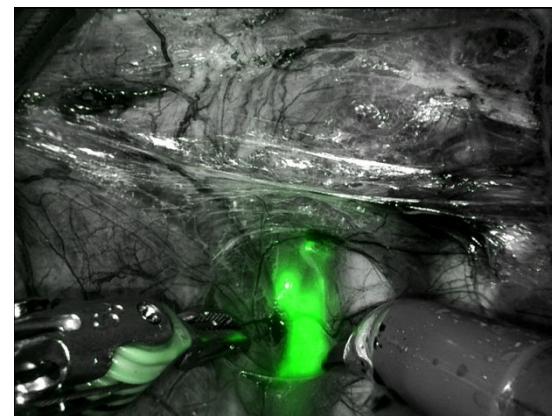
Bij deze schildwachtklierprocedure wordt straling gebruikt. Er bestaat een kleine kans dat de gebruikte straling leidt tot schade aan uw gezondheid. De schildwachtklierprocedure is standaard bij de behandeling van uw ziekte. Er is daarom bij deelname aan dit onderzoek geen extra risico door straling.

Welke nieuwe techniek gaan we onderzoeken?

Bij de nieuwe techniek wordt een groene stof ingespoten rondom de tumor. Dit gebeurt tijdens de operatie als u slaapt. De groene stof is niet zichtbaar met het blote oog, maar wel met een speciale camera. Wanneer deze camera wordt gebruikt, lichten de schildwachtklieren groen op. Op het plaatje hiernaast is te zien hoe dit eruit ziet.

Deze nieuwe techniek heeft voordelen. Zo wordt er geen straling gebruikt. Ook zijn allergische reacties zeer zeldzaam. De nieuwe techniek is minder belastend omdat een patiënt niet één dag voor de operatie al opgenomen moet worden in het ziekenhuis. We gaan onderzoeken of deze nieuwe techniek even goed werkt als de huidige techniek voor het vinden van de schildwachtklieren. Als dat zo is, dan kan deze nieuwe techniek de huidige techniek vervangen.

De groene stof is in Nederland nog niet geregistreerd voor het opsporen van schildwachtklieren. Er is wel al veel ervaring met deze stof. Zo wordt de groene stof al lange tijd gebruikt bij operaties aan bijvoorbeeld de ogen of de lever. Ook zijn er veel onderzoekers geweest die deze groene stof al veilig hebben gebruikt voor het opsporen van schildwachtklieren bij andere soorten kanker.



### 4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?

Doet u mee met het onderzoek? Dan kost dat u geen extra tijd. Het onderzoek vindt plaats tijdens de standaard behandeling.

Stap 1: bent u geschikt om mee te doen?

De gegevens van de afspraak met uw arts en de uitslagen van alle standaardonderzoeken hebben bepaald dat u geschikt bent om mee te doen aan dit onderzoek.

Stap 2: hoe verloopt de operatie?

Als u meedoet aan dit onderzoek, gebruikt uw arts de nieuwe techniek voor het opsporen van de schildwachtklieren. Daarnaast gebruikt uw arts ook nog de huidige techniek. Hierdoor kan de werking van beide technieken worden vergeleken.

De groene stof is onderdeel van de nieuwe techniek. Deze stof wordt ingespoten als u onder narcose bent. Tijdens de operatie wordt een speciale camera gebruikt om de schildwachtklieren

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op te sporen. U zult hier niets van merken. Verder verloopt de operatie zoals gebruikelijk is in uw ziekenhuis.

### *Stap 3: wat gebeurt er na de operatie?*

De zorg na de operatie blijft zoals die nu is. Er zijn geen extra controles nodig. Wel vragen we u één keer een vragenlijst in te vullen. Dit mag tijdens uw opname in het ziekenhuis of wanneer u weer thuis bent. Deze vragenlijst gaat over hoe u de zorg rondom de operatie heeft ervaren. De uitkomsten helpen ons om de behandeling en de zorg van baarmoederhalskanker verder te verbeteren.

In het plaatje hieronder ziet u het verloop van dit onderzoek.



## 5. Welke afspraken maken we met u?

We willen graag dat het onderzoek goed verloopt. Daarom maken we de volgende afspraken met u:

- U bespreekt met uw arts of de onderzoeker als u nog aan een ander medisch-wetenschappelijk onderzoek wil meedoen;
- U kan de week na de schildwachtklierprocedure geen schildkliertesten ondergaan. De reden hiervoor is dat er jodium in de groene stof zit. Dit kan de schildkliertest beïnvloeden.
- U neemt contact op met de onderzoeker in deze situaties:
  - U wordt in een ziekenhuis opgenomen;
  - U krijgt plotseling problemen met uw gezondheid;
  - U wilt niet meer meedoen met het onderzoek;
  - Uw telefoonnummer, adres of e-mailadres verandert.

## 6. Van welke bijwerkingen of nadelige effecten kunt u last krijgen?

Het gebruik van de nieuwe techniek kent geen bijwerkingen. Wel kan er in zeldzame gevallen een allergische reactie optreden. Een allergische reactie op de groene stof komt minder dan 1 op de 10.000 keer voor.

Wij verzoeken u onmiddellijk contact opnemen met de onderzoeker als u last krijgt van een allergische reactie. De klachten hiervan kunnen zijn: verhoogde hartslag, kortademigheid, opzwellingen van het gezicht, duizeligheid, misselijkheid, pijn in de borststreek, rusteloosheid, gevoel van warmte, jeuk, galbulten en/of blozen. De meeste allergische reacties treden op binnen enkele minuten of enkele dagen. Dat betekent dat u dan nog op de operatiekamer of de verpleegafdeling bent. In dat geval zijn er altijd zorgverleners in de buurt als u een



1  
2 allergische reactie krijgt.  
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## 5 **7. Wat zijn de voordelen en nadelen van meedoen aan het onderzoek?**

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7  
8

9 Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op  
10 een rij. Denk hier goed over na, en praat erover met anderen.  
11  
12

13 U heeft een mogelijk voordeel van meedoen. Met de extra groene stof kunnen we de  
14 schildwachtklieren mogelijk makkelijker opsporen, maar dat is niet zeker. Met uw deelname  
15 helpt u mee in de zoektocht naar een betere schildwachtklierprocedure voor vrouwen met  
16 baarmoederhalskanker.  
17  
18

19 Een nadeel van meedoen aan het onderzoek is dat de duur van de operatie ongeveer 15  
20 minuten langer kan zijn. Dat is maar een klein deel van de totale duur van de operatie van  
21 ongeveer vier uur. De risico's van langere narcose zijn zeer laag. U kunt ook last krijgen van  
22 een allergische reactie op de nieuwe techniek, zoals beschreven in paragraaf 6.  
23  
24

### 25 *Wilt u niet meedoen?*

26  
27

28 U beslist zelf of u meedoet aan het onderzoek. Wilt u niet meedoen? Dan ondergaat u op de  
29 gebruikelijke manier de schildwachtklierprocedure.  
30  
31

## 32 **8. Wanneer stopt het onderzoek?**

33  
34

35 De onderzoeker laat het aan u weten als er nieuwe informatie over het onderzoek is die  
36 belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.  
37  
38

39 In deze situaties stopt voor u het onderzoek:  
40  
41

- 42 • De operatie is klaar en u heeft de vragenlijst ingevuld.
- 43 • U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij  
44 de onderzoeker en uw arts. U hoeft er niet bij te vertellen waarom u stopt. Als u op het moment  
45 van stoppen de schildwachtklierprocedure nog moet ondergaan, krijgt u de gewone  
46 schildwachtklierprocedure voor baarmoederhalskanker. De nieuwe techniek wordt dan niet  
47 gebruikt.
- 48 • De onderzoeker vindt het veiliger voor u om te stoppen.
- 49 • Een van de volgende instanties besluit dat het onderzoek moet stoppen:
  - 50 o het UMC Utrecht,
  - 51 o de overheid, of
  - 52 o de medisch-ethische commissie die het onderzoek beoordeelt.

### 53 *Wat gebeurt er als u stopt met het onderzoek?*

54  
55

56 De onderzoekers gebruiken de gegevens die tot het moment van stoppen zijn  
57 verzameld.  
58  
59

60 Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.  
61  
62

## 63 **9. Wat gebeurt er na het onderzoek?**

64  
65

### 66 *Krijgt u de resultaten van het onderzoek?*

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68

69 Na de operatie kan uw arts u vertellen hoe de vergelijking van beide technieken is gegaan. Als  
70 het hele onderzoek is afgelopen, laat de onderzoeker u weten wat de belangrijkste uitkomsten  
71 zijn van het onderzoek. Wilt u dit niet weten? Zeg dat dan tegen uw arts of de onderzoeker.  
72 Hij/zij zal het u dan niet vertellen.  
73  
74



## 10. Wat doen we met uw gegevens?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?

We bewaren deze gegevens:

- uw naam;
- uw geboortedatum;
- uw e-mailadres;
- gegevens over uw gezondheid;
- (medische) gegevens die we tijdens het onderzoek verzamelen.

Waarom verzamelen, gebruiken en bewaren we uw gegevens?

We verzamelen, gebruiken en bewaren uw gegevens om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten openbaar te kunnen maken.

Hoe beschermen we uw privacy?

Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het ziekenhuis. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en openbare artikelen over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?

Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- Leden van de commissie die de veiligheid van het onderzoek in de gaten houdt;
- Een controleur die voor het UMC Utrecht werkt;
- Nationale en internationale toezichthoudende autoriteiten. Bijvoorbeeld de Inspectie Gezondheidszorg en Jeugd.

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens?

We bewaren uw gegevens 25 jaar in het ziekenhuis.

Mogen we uw gegevens gebruiken voor ander onderzoek?

Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander wetenschappelijk onderzoek op het gebied van baarmoederhalskanker. Daarvoor zullen uw gegevens 25 jaar worden bewaard in het ziekenhuis. In het toestemmingformulier geeft u aan of u dit goed vindt. Geeft u geen toestemming? Dan kunt u nog steeds meedoen met dit onderzoek. U krijgt dezelfde zorg.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?

U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Dit geldt voor het gebruik in dit onderzoek en voor het gebruik in ander onderzoek. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.



1  
2     *Wilt u meer weten over uw privacy?*

- 3  
4     • Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op  
5     [www.autoriteitpersoonsgegevens.nl](http://www.autoriteitpersoonsgegevens.nl).
- 6  
7     • Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw  
8     persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de  
9     verwerking van uw persoonsgegevens. Voor dit onderzoek is dat:  
10       o       UMC Utrecht. Zie **bijlage A** voor contactgegevens en website.

- 11  
12     • Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om  
13     deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris  
14     Gegevensbescherming van uw instelling gaan. Zie **bijlage A** voor de contactgegevens. Of u  
15     dient een klacht in bij de Autoriteit Persoonsgegevens.  
16

17     *Waar vindt u meer informatie over het onderzoek?*

18  
19     Op de volgende website(s) vindt u meer informatie over het onderzoek: [www.trialregister.nl](http://www.trialregister.nl).  
20     Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek  
21     tonen. U vindt het onderzoek door te zoeken op 'FluoreSENT study' (nummer: NL9011).  
22

## 23     **11. Krijgt u een vergoeding als u meedoet aan het onderzoek?**

24  
25     De nieuwe techniek die wordt gebruikt in het onderzoek kost u niets. U krijgt ook geen  
26     vergoeding als u meedoet aan dit onderzoek.  
27

## 28     **12. Bent u verzekerd tijdens het onderzoek?**

29  
30     Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. Dit is wettelijk  
31     verplicht. De verzekering betaalt voor schade door het onderzoek. Maar niet voor alle schade.  
32     In **bijlage B** vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook  
33     aan wie u schade kunt melden.  
34

## 35     **13. We informeren uw huisarts**

36  
37     De onderzoeker stuurt uw huisarts een brief om te laten weten dat u meedoet aan het  
38     onderzoek. Dit is voor uw eigen veiligheid. Als het nodig is kunnen we contact opnemen met  
39     uw huisarts, bijvoorbeeld over uw medische geschiedenis of over de medicijnen die u gebruikt.  
40

## 41     **14. Heeft u vragen?**

42  
43     Vragen over het onderzoek kunt u stellen aan de onderzoeker. Wilt u advies van iemand die  
44     er geen belang bij heeft? Neem dan contact op met de onafhankelijk arts dhr. Ruurda. Hij  
45     weet veel over het onderzoek maar werkt niet mee aan het onderzoek. Heeft u een klacht?  
46     Bespreek dit dan met de onderzoeker of uw eigen arts. Wilt u dit liever niet? Ga dan naar de  
47     klachtencommissie van uw ziekenhuis. In **bijlage A** staat waar u die kunt vinden.  
48

## 49     **15. Hoe geeft u toestemming voor het onderzoek?**

50  
51     U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de  
52     informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het  
53     toestemmingsformulier in dat u achteraan deze informatiebrief vindt. U en de onderzoeker  
54     krijgen allebei een getekende versie van deze toestemmingsverklaring.  
55

56  
57     Dank voor uw aandacht. We zijn dankbaar dat u wil nadenken over meedoen met dit  
58     onderzoek.  
59

60     Namens het FluoreSENT onderzoeksteam

Namens het FluoreSENT onderzoeksteam

Kees Gerestein, gynaecologisch oncoloog



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**16. Bijlagen bij deze informatie**

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7 A. Contactgegevens UMC Utrecht  
8 B. Toestemmingsformulier(en)  
9 C. Informatie over de verzekering  
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For peer review only



## Bijlage A: contactgegevens voor het UMC Utrecht

### Contactpersoon onderzoek:

Drs. Ilse Baeten, arts-onderzoeker

Postbus 85500

3508 GA Utrecht

Telefoonnummer 088 75 530 68

E-mail [i.g.t.baeten@umcutrecht.nl](mailto:i.g.t.baeten@umcutrecht.nl)

Bereikbaar van maandag t/m vrijdag

### Hoofdonderzoeker:

Dr. Kees Gerestein, gynaecologisch oncoloog

Postbus 85500

3508 GA Utrecht

Telefoonnummer 088 75 564 27

Email [c.g.gerestein-2@umcutrecht.nl](mailto:c.g.gerestein-2@umcutrecht.nl)

### Onafhankelijk arts:

Prof. dr. Jelle Ruurda, chirurg

Postbus 85500

3508 GA Utrecht

Telefoonnummer 088 75 580 74

Email [j.p.ruurda@umcutrecht.nl](mailto:j.p.ruurda@umcutrecht.nl)

### Klachten:

Klachtenbemiddeling UMC Utrecht

Huispost D01.343

Antwoordnummer 8419

Postbus 85500

3508 GA UTRECHT

Telefoonnummer 088 75 562 08

[www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klacht-indienen](http://www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klacht-indienen)

### Functionaris voor de Gegevensbescherming van de instelling:

UMC Utrecht t.a.v. Functionaris gegevensbescherming

Huispost Fac. 10.12

Postbus 85500

3508GA Utrecht

Email [privacy@umcutrecht.nl](mailto:privacy@umcutrecht.nl)

<https://www.umcutrecht.nl/nl/Over-Ons/Privacy>



## Bijlage B: toestemmingsformulier deelnemer aan deze studie

Behorende bij: **Een nieuwe techniek voor het opsporen van schildwachtklieren**

*Met als officiële titel:* De bilaterale schildwachtklier detectie van fluorescent indocyanine groen in vergelijking met technetium-99m en blauw in de schildwachtklierprocedure in stadium I-IIA cervixcarcinoom: de FluoreSENT studie

Lees dit formulier rustig door. Bij tekenen van het formulier bent u het eens met de onderstaande punten:

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts te laten weten dat ik meedoet aan dit onderzoek.
- Ik geef de onderzoekers toestemming om mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.

- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja <input type="checkbox"/>	Nee <input type="checkbox"/>
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja <input type="checkbox"/>	Nee <input type="checkbox"/>

- Ik wil meedoen aan dit onderzoek.

Mijn naam is (deelnemer): .....

Handtekening: .....

Datum : \_\_ / \_\_ / \_\_

-----  
Ik verklaar dat ik deze deelnemer volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die de toestemming van de deelnemer kan beïnvloeden? Dan laat ik dit op tijd weten aan deze deelnemer.

Naam onderzoeker (of diens vertegenwoordiger):.....

Handtekening:.....

Datum: \_\_ / \_\_ / \_\_

De deelnemer aan deze studie krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.



## Bijlage C: informatie over de verzekering

Het UMC Utrecht heeft een verzekering afgesloten voor iedereen die meedoet aan het onderzoek. De verzekering betaalt de schade die u heeft doordat u aan het onderzoek meedeed. Het gaat om schade die u krijgt tijdens het onderzoek, of binnen 4 jaar na het onderzoek. U moet schade binnen 4 jaar melden bij de verzekeraar.

Heeft u schade door het onderzoek? Meld dit dan telefonisch of per post bij deze verzekeraar:

De verzekeraar van het onderzoek is:

Naam: CNA Insurance Company Ltd

Adres: Strawinskylaan 703, 1077 XX, Amsterdam, Nederland

Telefoonnummer: +31 (0)20 57 37 274

Polisnummer: 10201366

Contactpersoon: Mw. Esther van Herk

De verzekering betaalt maximaal € 650.000 per persoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.

Let op: de verzekering dekt de volgende schade niet:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat u aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van uw kinderen of kleinkinderen.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (<https://wetten.overheid.nl>).



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item No	Item	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <b>Manuscript page 1</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <b>Netherlands Trial Registry: number NL9011 (see Page 2).</b>
	2b	All items from the World Health Organization Trial Registration Data Set <b>For the Netherlands the NTR is the Primary Registry accepted by the WHO and ICMJE.</b>
Protocol version	3	Date and version identifier <b>01-07-2021 / NL75722.041.20 / version 1.4</b>
Funding	4	Sources and types of financial, material, and other support <b>Funding, manuscript page 11</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <b>Check (described on title page of study protocol)</b>
	5b	Name and contact information for the trial sponsor <b>Check; UMC Utrecht (described in study protocol)</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <b>Check (described in study protocol)</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <b>Check (described in study protocol)</b>

**Introduction**

1	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <b>Introduction, manuscript page 3 - 5</b>
2		6b	Explanation for choice of comparators <b>Introduction, manuscript page 3 – 5</b>
3	Objectives	7	Specific objectives or hypotheses <b>Introduction, page 3 – 5, and Statistical analysis, manuscript page 10</b>
4			
5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <b>Methods, Study design, manuscript page 5</b>
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## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <b>Methods, Study population, manuscript page 5</b>
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <b>Methods, Study design and Study population, manuscript page 5-6</b>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <b>Methods, manuscript page 7</b>
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <b>Not applicable</b>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <b>Not applicable</b>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <b>Methods, Trial intervention, manuscript page 7</b>

1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <a href="#">Methods, Outcomes, manuscript page 8</a>
11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <a href="#">See flow chart in Figure 1 of the manuscript</a>
17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <a href="#">Methods, Sample size, manuscript page 6</a>
22	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <a href="#">Check (recruitment and informed consent procedure are described in study protocol)</a>

### 28 Methods: Assignment of interventions (for controlled trials)

#### 30 Allocation:

32	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions <a href="#">Not applicable</a>
42	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned <a href="#">Not applicable</a>
49	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions <a href="#">Not applicable</a>
53	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Not applicable</a>

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2      17b If blinded, circumstances under which unblinding is permissible, and  
3                    procedure for revealing a participant's allocated intervention during  
4                    the trial  
5                    Not applicable  
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7      **Methods: Data collection, management, and analysis**  
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10     Data collection methods      18a Plans for assessment and collection of outcome, baseline, and other  
11                    trial data, including any related processes to promote data quality (eg,  
12                    duplicate measurements, training of assessors) and a description of  
13                    study instruments (eg, questionnaires, laboratory tests) along with  
14                    their reliability and validity, if known. Reference to where data  
15                    collection forms can be found, if not in the protocol  
16                    **Methods, Data collection and management, manuscript page 9**  
17  
18     Data management      19      Plans for data entry, coding, security, and storage, including any  
19                    related processes to promote data quality (eg, double data entry;  
20                    range checks for data values). Reference to where details of data  
21                    management procedures can be found, if not in the protocol  
22                    **Methods, Data collection and management, manuscript page 9. Also,**  
23                    **there is a reference to Datamanagement plan in study protocol.**  
24  
25     Statistical methods      20a     Statistical methods for analysing primary and secondary outcomes.  
26                    Reference to where other details of the statistical analysis plan can be  
27                    found, if not in the protocol  
28                    **Methods, Statistical analysis, manuscript page 10**  
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30          20b      Methods for any additional analyses (eg, subgroup and adjusted  
31                    analyses)  
32                    **Methods, Statistical analysis, manuscript page 10**  
33  
34          20c      Definition of analysis population relating to protocol non-adherence  
35                    (eg, as randomised analysis), and any statistical methods to handle  
36                    missing data (eg, multiple imputation)  
37                    **Check (handling missing data is described in study protocol).**  
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48      **Methods: Monitoring**  
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- 50     Data monitoring      21a     Composition of data monitoring committee (DMC); summary of its role  
51                    and reporting structure; statement of whether it is independent from  
52                    the sponsor and competing interests; and reference to where further  
53                    details about its charter can be found, if not in the protocol.  
54                    Alternatively, an explanation of why a DMC is not needed  
55                    **Methods, Data collection and management, manuscript page 9.**  
56                    **Independent monitor has been assigned.**  
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1	21b	Description of any interim analyses and stopping guidelines, including 3 who will have access to these interim results and make the final 4 decision to terminate the trial  <b>Not applicable</b>
7	Harms	22 Plans for collecting, assessing, reporting, and managing solicited and 8 spontaneously reported adverse events and other unintended effects 9 of trial interventions or trial conduct  <b>Check (described in study protocol according to the CCMO 10 guidelines)</b>
14	Auditing	23 Frequency and procedures for auditing trial conduct, if any, and 15 whether the process will be independent from investigators and the 16 sponsor  <b>Check (reference to written monitor plan in protocol)</b>
<b>Ethics and dissemination</b>		
22	Research ethics approval	24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval  <b>Approval has been obtained.</b>
27	Protocol amendments	25 Plans for communicating important protocol modifications (eg, 28 changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, 30 regulators)  <b>Check (described in study protocol according to the CCMO 32 guidelines)</b>
35	Consent or assent	26a Who will obtain informed consent or assent from potential trial 36 participants or authorised surrogates, and how (see Item 32)  <b>Check (recruitment and informed consent procedure are described 38 in study protocol)</b>
41		26b Additional consent provisions for collection and use of participant data 42 and biological specimens in ancillary studies, if applicable  <b>Not applicable</b>
45	Confidentiality	27 How personal information about potential and enrolled participants will 46 be collected, shared, and maintained in order to protect confidentiality 47 before, during, and after the trial  <b>Check (reference to written Datamanagement plan in study protocol)</b>
51	Declaration of interests	28 Financial and other competing interests for principal investigators for 52 the overall trial and each study site  <b>Competing interests, manuscript page 12</b>
55	Access to data	29 Statement of who will have access to the final trial dataset, and 56 disclosure of contractual agreements that limit such access for 57 investigators  <b>Check (reference to written Datamanagement plan in study protocol)</b>

- 1 Ancillary and  
2 post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for  
3 compensation to those who suffer harm from trial participation  
4 **Check (liability insurance and participant insurance are taken out by  
5 the study sponsor)**
- 6 Dissemination  
7 policy 31a Plans for investigators and sponsor to communicate trial results to  
8 participants, healthcare professionals, the public, and other relevant  
9 groups (eg, via publication, reporting in results databases, or other  
10 data sharing arrangements), including any publication restrictions  
11 **Check (written Dissemination plan)**
- 12 31b Authorship eligibility guidelines and any intended use of professional  
13 writers  
14 **Check**
- 15 31c Plans, if any, for granting public access to the full protocol, participant-  
16 level dataset, and statistical code  
17 **Check (reference to written Datamanagement plan in study protocol)**

## 23 Appendices

- 24 Informed consent 32 Model consent form and other related documentation given to  
25 materials participants and authorised surrogates  
26 **Check (added the MREC approved model as supplementary file)**
- 27 Biological 33 Plans for collection, laboratory evaluation, and storage of biological  
28 specimens specimens for genetic or molecular analysis in the current trial and for  
29 future use in ancillary studies, if applicable  
30 **Not applicable**

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