



**THE SPIES NON-MUSCLE-INVASIVE BLADDER CANCER STUDY – A MULTICENTER
RANDOMIZED CONTROLLED STUDY**

**A Multicenter International Randomized Controlled Study to compare the outcome
using the Storz Professional Image Enhancement System (SPIES) versus White Light
Imaging (WLI) during TURB of Non-Muscle-Invasive Bladder Cancer (NMIBC).**

Protocol ID: NL50451.018.14 - SPIES vs WL RCT

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PROTOCOL SIGNATURE PAGE

SPONSOR REPRESENTATIVE

Name:

Date:

Signature:

INVESTIGATOR(S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated by CROES, with or without cause.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments. I assure a successor will be appointed if I leave the study site before this investigation has ended, and that my successor will sign this agreement.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I will ensure that the requirements relating to Medical Ethics Committee (MEC) review and approval are met. I will provide CROES with any material, which is provided to the MEC for ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the MEC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not

make any changes in the research without MEC approval, except where necessary to ensure the safety of study participants.

This clinical trial protocol is the property of CROES and may not be used or published without their consent. The data from the patients included are property of CROES and may only be used following given consent by CROES council.

Name:

Date:

Signature:

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

(S)AE	(Serious) Adverse Event
BMI	Body Mass Index
CIS	Carcinoma In Situ
(e)CRF	(electronic) Case Report Form
CROES	Clinical Research Office of the Endourological Society
DMS	Data Management System
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine Device
IVU	Intravenous Urogram
MEC	Medical research Ethics Committee
NBI	Narrow Band Imaging
NMIBC	Non-Muscle-Invasive Bladder Cancer
PI	Principal Investigator
SPIES	
	Storz Professional Image Enhancement System
TURB	TransUrethral Resection of the Bladder
UC	Urothelial Carcinoma
WL(I)	White Light (Imaging)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Urothelial carcinoma of the bladder has a high recurrence rate, partly due to missed lesions at diagnostics with White Light Imaging (WLI) cystoscopy. Storz Professional Image Enhancement System (SPIES) is a new technique that visually enhances the images in order to improve diagnostic accuracy. SPIES assisted TURBs are expected to result in lower recurrence rates of bladder tumor compared with White Light TURBs.

Objective: To compare the recurrence rate of tumor at 12 months following SPIES assisted TURB with WLI assisted TURB in patients with non-muscle invasive bladder cancer (NMIBC Ta/T1/CIS).

Study design: This study is a multicenter randomized controlled trial in which the efficacy between SPIES assisted and WLI assisted TURB are compared. Subjects in the experimental arm (Arm A) will undergo SPIES assisted TURB, whereas subjects in the control arm (Arm B) will receive treatment with WLI assisted TURB only. Baseline characteristics will be recorded, as well as short and long-term follow up.

Study population: The study population comprises those patients who are presenting with primary or recurrent urothelial bladder cancer (NMIBC stage Ta, T1 or CIS) in the participating centers.

Intervention: All patients will undergo TURB. Patients in Arm A will undergo SPIES and WLI assisted TURB, and patients in Arm B will undergo WLI only assisted TURB.

Main study parameters/endpoints: Primary end point of the study is recurrence rate of tumor at 12 months after TURB in the two arms. Secondary end points include recurrence rates at 3 months and 3 years.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risk associated with participating in this trial does not differ for patients in the experimental or the control arm. In both groups patients will undergo TURB, and will be followed for a maximum of three years at several site visits, in accordance with existing guidelines for follow up.

1. INTRODUCTION AND RATIONALE

Urothelial carcinoma (UC) develops in the bladder and the upper urinary tract (UUT). Non-muscle-invasive bladder cancer (NMIBC) includes stages Ta, T1 and carcinoma in situ (CIS) and it accounts for 75% of primary diagnosed bladder tumors. Recurrence rates of UC are exceptionally high, which calls for extensive diagnostics and surveillance strategies.

Percentages on recurrence from EORTC studies have been estimated to range from 15% to 61% at one year after surgery. Risk for recurrence is associated with stage, grade and number of tumors, while progression is associated with grade and the presence of CIS (Sylvester et al., 2006).

Diagnostics of UC of the bladder is usually performed by the visual approach including the need for biopsies or transurethral resection of the bladder (TURB). Most tumors can be identified by White Light (WL) cystoscopy. However, especially CIS is difficult to identify using this procedure. Non-identified tumors can later appear as recurrence, some of which becoming invasive. This demonstrates the need for a procedure that more accurately detects bladder tumors. Since a more accurate detection of tumors leads to more targeted treatment and better complete resection, the rate of recurrence may decrease with such procedures.

The use of photodynamic agents e.g. HEXVIX has been shown to be helpful in these cases in order to accomplish a better resection, identify “overlooked” tumors, and to target biopsies in case of a positive cytology only. This translates into more complete resection, reducing the recurrence rate of non-invasive tumors (Stenzl et al., 2010) and in more appropriate treatments (Mowatt et al., 2011). The technique of Narrow Band Imaging (NBI) is being studied at the moment. This technique uses a light filter, which results in enhancement of the fine structures of the mucosal surface (Cauberg et al., 2010). KARL STORZ has developed a new technique that is now ready for clinical evaluation. With Storz Professional Image Enhancement System (SPIES), no endoscopic filter is needed to enhance the image in order to gain more clarity. SPIES is based on a new software platform, which uses the different light wavelengths to produce images with different contrast specifications. SPIES offers a technique which could be useful in bladder cancer treatment, since clearer images are likely to result in reducing the numbers of tumors that are missed by the gold standard White Light Imaging (WLI). Additionally, once the tumor is detected, SPIES images may help find the demarcation between tumor and healthy tissue, resulting in more complete resection of the tumor(s). The Clinical Research Office of the Endourological Society (CROES) has initiated this study, because patients could benefit from better imaging during TURB. The recurrence

rate is expected to be decreased with the use of SPIES by obtaining a more complete resection, meaning the patient will need less invasive diagnostic and surgical visits.

2. OBJECTIVES

Primary Objective:

1. To compare the recurrence rate of tumor at 12 months following SPIES assisted TURB (Arm A) with White Light Imaging only assisted TURB (Arm B) in patients with primary or recurrent non-muscle-invasive urothelial bladder cancer (NMIBC Ta/T1/CIS). A subgroup analysis will be carried out for patients presenting with only primary tumors.

Secondary Objectives:

1. To assess the recurrence rate of tumor at short and long term follow up (3 months and 3 years) after SPIES or WLI assisted TURB in patients with NMIBC.
2. To assess the peri-operative morbidity (30 days) between SPIES and WLI assisted TURB by comparing the proportion of adverse events and using the Clavien-Dindo score.

2.1 Study design

This study is a multicenter randomized controlled trial in which the recurrence rates of cancer between SPIES assisted and WLI assisted TURB are compared. Randomization is stratified by tumor multiplicity (single or multiple), tumor status (primary or recurrent) and macroscopic findings (papillary or flat, where CIS is scored as flat lesion). Patients randomized into the experimental arm (Arm A) will undergo SPIES and WLI assisted TURB, whereas the patients in the control arm (Arm B) will undergo WLI only assisted TURB. WLI is chosen as control, since it is considered the gold standard for detecting bladder tumors. Short and long term follow up will be recorded in order to evaluate the health gains for patients over a longer period. Perioperative (30 days) complications will be compared between the two treatment arms to evaluate the safety of SPIES.

Each participating center must submit this protocol to their local MEC and each participating center is responsible for the insurance of their patients. Data from all participating centers will be collected through electronic Case Report Forms (eCRFs), with use of an online Data Management System (DMS), which is located and maintained at the CROES office.

Members of the CROES office will perform all analyses. Each center willing to participate should have enough experience and be familiar with SPIES. A center is considered to have enough experience when a minimum of 10-20 procedures have already been done with SPIES prior to including patients in this study.

2.2 Population

The study population comprises those adults (aged 18 years or above) who are presenting with primary or recurrent urothelial bladder cancer in the participating centers (NMIBC: Ta/T1/CIS). Patients are supposed to have been diagnosed with NMIBC after WL exploration a maximum of 30 days before inclusion in the study. Participating centers are those that have been selected to take part in this study. All are academic centers where primary health care is provided.

2.3 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Has signed informed consent
- Is scheduled for treatment of a primary or recurrent NMIBC
- Is aged 18 years or older
- Has or has had no tumors in the upper urinary tract
- Has had no previous irradiation of the pelvis

2.4 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Gross haematuria at the time of TURB (i.e. heavy bladder bleeding resulting in marked amounts of blood in the urine which may interfere with cystoscopy)
- Participation in other clinical studies with investigational drugs either concurrently or within the last 30 days
- Pregnancy or breast-feeding (all women of child-bearing potential must document a negative serum or urine pregnancy test at screening and are suggested to use the contraceptive pill or an intrauterine device (IUD) during the treatments and for at least one months thereafter)
- Conditions associated with a risk of poor protocol compliance
- Has had instillation therapy in the six months prior to the screening visit

2.5 Justification of sample size

Sample size is based on the subgroup analysis of patients with primary tumors. The normal approximation to the binomial distribution was used, using continuity corrected Chi square test for proportions, and the following specifications were set:

- a. Randomization rate between the two arms= 1:1

- b. Clinically relevant difference in recurrence detection rates $\geq 10\%$
- c. Significance level (α - two sided) = 5%
- d. Power ($1-\beta$) = 80%
- e. Expected recurrence rate at 1 year in the control arm (Arm B) = 35% (Babjuk et al., 2013).

The required sample size per arm is calculated to be 349 patients, which leads to a total of at least 698 patients needed to detect the difference in proportions stated above for the subgroup analysis of only patients with primary tumors. Since we expect approximately 15% of the patients to be misdiagnosed, and thus not suitable to our research question, the number of patients is inflated with that percentage, leading to 401 patients per arm. Additionally, to allow for a non-compliance rate of 20%, assuming no cross-over and no differential loss to follow up between the arms, the calculated sample size is inflated by 20%, yielding 482 patients per arm. Since approximately $\frac{1}{2}$ of all patients will be patients with primary tumors, this sample size is multiplied by two, leading to a total sample size of 1,928. Sample size calculation was performed using nQuery Advisor 7.0.

TREATMENT OF SUBJECTS

2.6 Investigational treatment

White Light cystoscopy (WL) is currently the gold standard for detecting and treatment of bladder cancer during transurethral resection of the bladder (TURB). Storz Professional Image Enhancement System (SPIES) is a new technique, which visually enhances the contrast between tumor mucosa and healthy tissue, in order to improve the sensitivity of tumor detection.

2.7 Use of co-intervention

Women of childbearing potential are recommended to use the contraceptive pill or intrauterine device during the treatments and for at least one month thereafter. It is a necessity to stop anticoagulation use during the procedure. Anticoagulation can be stopped according to the protocol of the hospital; any deviations from this protocol will be registered.

2.8 Name and description of investigational product

SPIES is a new endoscopic technique which does not require special filters for optimizing visibility of bladder tumors, but instead uses specially designed software to enhance the contrast in the endoscopic image between tumor tissue and healthy tissue. With use of color component processing, the red spectral distribution is suppressed, after which a three-color image is built from the blue and green spectral input. This results in a higher color contrast for differences in the blue and green spectrum, which is related to haemoglobin. Due to its nature and appearance, especially carcinoma in situ (CIS) is expected to be better detectable using SPIES, as compared with WLI. During endoscopy, surgeons can switch between WLI and SPIES and vice versa to study a tumor to their best ability.

2.9 Summary of findings from non-clinical studies

The quality of vision with SPIES has been examined in the iSPIES Study. In this study, urologists were asked to delineate tumors that were shown on images from different modalities of SPIES and WL. Inter and intra-observer variability will be assessed based on an objective measurement. Data from this study is currently being analysed, and will be prepared for publication soon.

2.10 Summary of findings from clinical studies

Diagnostic accuracy is expected to be improved using SPIES compared with WLI, but has not yet been tested clinically.

2.11 Summary of known and potential risks and benefits

The risks patients are subject to in this trial do not differ from risks associated with non-experimental surgery for this condition. Patients will receive the standard treatment in addition to the extra care that is provided to them in the framework of this study. Patients in the experimental arm could have added value from imaging with use of SPIES, since it is expected to improve the sensitivity of the diagnostic tool for assessing bladder cancer.

3. METHODS

3.1 Study parameters/endpoints

3.1.1 Main study parameter/endpoint

- Comparison of the proportions of Arm A and Arm B subjects who undergo TURB for a Ta, T1 or CIS bladder tumor that have a histologically confirmed recurrence found at either three months, one year and three years after TURB.

3.1.2 Secondary study parameters/endpoints

- Peri-operative morbidity (30 days) assessed by the Clavien-Dindo score
- Proportion of re-TUR (defined as within 3 months of initial TURB: this can be a planned TURBT because of resection of high risk tumor, or because of recurrent tumor confirmed at cystoscopy at three months)

3.1.3 Other study parameters

- Baseline characteristics of the patients, such as age or BMI
- Comorbidities, such as Diabetes Mellitus or cardiovascular disease
- Risk factors, such as smoking and use of anticoagulation
- When appropriate: information on previous (adjuvant) treatment, such as type and date of most recent treatment and re-TURs

3.2 Assessment of safety and efficacy

Safety will be determined by assessment of adverse events, vital signs and limited physical examination. In addition, the following will be recorded: complications during surgery, use of bipolar or monopolar TURB, use of platform SPIES (when appropriate), operating time and length of stay.

3.3 Randomisation and treatment allocation

Patients presenting with a bladder cancer and who are scheduled for TURB or patients who are scheduled for random biopsies and/or TURB because of a bladder wash out or voided urine with malignant (G3) cells will be included in the study. Eligible patients who are willing to participate will be randomized in a ratio of 1:1 to either Arm A (SPIES+WLI assisted TURB) or Arm B (WLI assisted TURB). The CROES will utilize the randomization to minimize systematic error and potential selection bias by the investigators. The randomization will be performed by using randomly permuted blocks (computer generated), with block size of 6. To assure balanced characteristics and comparable prognosis between the two arms, the

randomization will be stratified on tumor multiplicity (single or multiple), tumor status (primary or recurrence) and macroscopic findings at time of baseline visit (papillary or solid/flat tumor [including CIS]), leading to 8 stratification groups.

Concealment of treatment allocation is achieved by: 1) reducing the time between randomization and intervention, 2) first deciding whether the patient meets all study entry criteria, and 3) if so, randomize the patient in the DMS. The randomization will take place just before the intervention starts; ideally both occur on the same day. The DMS performs the randomization then reveals treatment allocation. The patients will be blinded to their allocation. Due to the nature of the procedure, the surgeon will not be blinded.

3.4 Study procedure

3.4.1 Diagnosis and Pre-treatment evaluation – Visit 1

Patients eligible for screening will be informed about this study as soon as they are being scheduled for TURB. Pre-treatment evaluation at Visit 1 will only be performed after the patient has agreed to participate and has signed and dated the informed consent form. No treatment will be initiated before informed consent has been given. Pre-treatment evaluation will be performed based on the study inclusion and exclusion criteria, including:

- Patient informed consent
- Demographics
- Medical history (including previous treatment for NMIBC)
- Urinalysis (including culture)
- Urine cytology
- Upper tract imaging: CT, IVU, MRI or US

The investigator/research nurse will complete a screening log of all patients who were approached to participate in the trial. This log contains the patients' initials, date of birth and date of visit. If the patient fails to enter the study, the reason(s) for not participating or non-eligibility will be documented.

If the patient enters the study, anticoagulation medication must be interrupted before surgery according to the protocol of the hospital. Anticoagulation medication may be re-continued after surgery according to hospital protocol.

3.4.2 Treatment with TURB – Visit 2

Following successful completion of the pre-treatment evaluation, patients will continue into the second visit. This consecutive visit may ideally be combined with Visit 1 and should at the latest take place within 14 days after Visit 1. This visit consists of the surgical procedure, and thus will include:

- Limited physical examination
- Examination of vital signs
- Recording of concomitant medication
- Assessment of bladder symptoms prior to TURB
- SPIES or WLI only assisted TURB

Peri-operative complications will be recorded when appropriate, up to 30 days of hospitalization. In addition, hospital stay and duration of operation will be recorded. When appropriate, (serious) adverse events ([S]AEs) will be recorded.

3.4.3 First follow up – three months after surgery – Visit 3

At three months after surgery, all patients will undergo a routine follow up using WLI cystoscopy. A two-week window will be allowed for the timing of this examination. All visible lesions should be confirmed histologically. Adjuvant treatment will be offered according to the local protocols. When appropriate, information on re-TUR and/or adjuvant treatment will be recorded, as well as adverse events. Information on re-TUR includes reasons for performing this procedure to determine if it was an incomplete resection or a true recurrence found at follow up. Information on adjuvant treatment includes type, timings, time limits and dose.

3.4.4 Intermediate follow up – 6, 9, 12, 18, 24 and 30 months after surgery – Visit 4 to 9

At the time points specified above, all patients will undergo a follow up using WLI cystoscopy. A four-week window will be allowed for the timing of this examination. All visible lesions should be confirmed histologically.

3.4.5 Last study follow up – three years after surgery – Visit 10

At three years after surgery, all patients will undergo a follow up using WLI cystoscopy. A four-week window will be allowed for the timing of this examination. All visible lesions should be confirmed histologically.

3.4.6 Biopsies and histology

Transurethral resection biopsies will be obtained from all flat lesions and suspicious areas. All papillary lesions must be resected completely. Tissue from the resected lesion(s) will be collected for histological assessment. The findings from both biopsies as well as resected lesions will be registered on a bladder chart and will include presence of lesion, size (defined as the diameter of the largest side of the tumor), type (papillary or flat), number of lesions and location (bladder neck anterior/posterior, trigone, around ureteric orifice right/left, posterior wall, right/left lateral wall, anterior wall, dome). The local pathologist will examine the samples. Staging of the tumors will be done according to the TNM 2009 classification

(Babjuk et al., 2013). Both WHO grading systems will be used for the report (2004 and 1973). For consistency, a standardized pathology procedure will be used to perform the analysis.

3.4.7 Concomitant medication

Any licensed concomitant medication required for the well-being of the patient is permitted. Anti-coagulation medication must be discontinued during surgery according to local protocol, but may be continued after the procedure. Concomitant medication usage will be documented at any visit during this trial.

3.4.8 Study duration (patient)

Patients participating in this study will undergo a screening visit, followed by SPIES or WLI assisted TURB. During TURB, cystoscopy will be performed and biopsies and resections will be taken for analysis. Several follow up visits will be planned (at three, six, nine and twelve months and 18, 24, 30 and 36 months after TURB) to check for possible recurrence of the tumors. Depending on the grade and stage of the (initial or recurrent) tumors, these visits could be scheduled more often if the treating physician deems necessary.

3.4.9 Study duration (investigator)

The number of centers participating in this study is 15. Each center is expected to recruit 100 patients a year. With the required number of patients being 1928, the estimated recruitment time is approximately one and a half year. Due to the maximum follow up of three years, the total study duration is expected to be four and a half years.

3.5 Surgery procedures

At Visit 2, as described in the preceding paragraphs, patients will undergo TURB. The procedure for TURB is described in this paragraph, for patients in both treatment Arm A and Arm B.

The following procedure will be utilized to accomplish the cystoscopic examination of each patient:

For patients allocated to treatment Arm A (SPIES):

1. Turn on the white light. Inspection of the bladder and indicating all papillary lesions and flat and suspicious lesions seen on a bladder diagram.

2. Turn to the SPIES software image. Inspection of the bladder and indicating all papillary lesions and flat and suspicious lesions seen on a bladder diagram (Appendix A). The choice of SPIES-platform (i.e. Clara, Chroma, Spectra A or Spectra B) is to the discretion of the investigator, and will be recorded. The use of the SPIES-VIEW mode, which provides two images at the same time (WL and SPIES) on the same screen, is allowed and is to the discretion of the investigator.
3. Perform complete resection (TURB) of all papillary lesions, and obtain biopsies of all flat lesions and suspicious areas. Choice of modality (SPIES or WL) for resection is to the discretion of the investigator, and will be recorded.

For patients allocated to treatment Arm B (WLI):

1. Turn on the white light. Inspection of the bladder and indicating all papillary lesions and flat and suspicious lesion seen on a bladder diagram (Appendix A).
2. Perform complete resection (TURB) of all papillary lesions, and obtain biopsies of all flat lesions and suspicious areas.
3. The patient will be treated to normal hospital routines

All positive or suspect areas will be resected or biopsied using WL or SPIES. All papillary lesions must be resected completely.

Adjuvant treatment is up to the local investigator, however we recommend standardization for low-, intermediate, and high-risk groups (as defined by EORTC).

3.6 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences and without providing reason(s) for withdrawal and without prejudices to further treatment. Completion or trial termination for any reason will be fully documented in the eCRF. The investigator can decide to withdraw a subject from the study for urgent medical reasons, which should be documented.

3.7 Follow-up of subjects withdrawn from trial

Subjects who are withdrawn from the study will be followed and checked according to the Good Clinical Practice (GCP) Guidelines for clinical trials.

4. SAFETY REPORTING

4.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited MEC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited MEC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

4.2 AEs, SAEs

4.2.1 Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded.

4.2.2 Serious adverse events

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All serious adverse events have to be reported to the sponsor within 24 hours, by fax or email or via a specific designed form.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited MEC that approved the protocol, to the competent authority, the Medicine Evaluation Board, and the competent authorities in other member states. The expedited reporting will occur within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

4.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

4.4 Source data identification

Patient information collected in the eCRF, but not recorded in the patients' file is regarded as source data. Information that should be collected in both the eCRF and the patient files include visit dates, safety data (including AEs and SAEs), withdrawal of consent, and any information on violating the study procedures prior to obtaining informed consent. Patients' files should also include a statement of participation in this trial, along with a copy of the signed informed consent form. Copies of biopsy report from local pathologists will be filed in the eCRF.

5. STATISTICAL ANALYSIS

5.1 Primary study parameters

The primary end point will be analysed by testing the following hypothesis.

The proportions of patients in either Arm A or Arm B who have recurrence of bladder cancer at one year after TURB will be compared. A two-sided test will be used, with the accompanying null-hypothesis being:

H_0 : The proportions of subjects with recurrence of bladder cancer at one year after TURB are equal for Arm A and Arm B, i.e. $H_0: \pi_A = \pi_B$;
with subsequently, $H_1: \pi_A \neq \pi_B$.

An intention-to-treat analysis will be performed, meaning that all subjects who were randomized will be included in the analyses.

5.2 Secondary study parameters

The secondary end points of this trial will be tested in the same manner as described for the primary end point. Additionally, the secondary objectives will be assessed with the appropriate tests for the different objectives.

5.3 Other study parameters

Multivariate analyses will be performed to assess possible associations with surgeon experience, geographical differences and risk factors for complications after surgery.

5.4 Handling missing and spurious data

When missing data occurs in the primary outcome variable, a sensitivity analysis will be performed. In the sensitivity analysis, the missing data at three months will be substituted by the value "recurrence", unless the result at later follow up is "no recurrence". Missing data at twelve months will be substituted by the value "recurrence", unless the result at later follow up is "no recurrence". Missing data at three years will be substituted by the value "recurrence". In the analyses of secondary objectives, analyses will be carried out on available data, with reporting of proportions of missing data.

All analyses will be performed using software SPSS 20, Stata 13 and R 3.0 or higher. Analysis will be based on the principle of intention-to-treat. All patients who signed the

informed consent form, met the study entry criteria and underwent randomization will be included in the analysis.

Results will be presented in tables reporting at least the number of subjects, mean, standard deviation, minimum and maximum for continuous data; and number of subjects and percentages for categorical data.

6. ETHICAL CONSIDERATIONS

6.1 Regulation statement

This study will be conducted in compliance with the current revision of the Declaration of Helsinki, ICH guidelines for Good Clinical Practice and applicable local regulatory requirements. This includes subjects' informed consent, investigator reporting requirements and IEC/IRB approval. A recognized IEC/IRB must approve this study and their approval of the final protocol is needed before this study may be started.

Copies of communications from the IEC/IRB to the investigator should be available, indicating approval of the study prior to its initiation. Subsequently, the investigator should submit written summaries of the status of the study to the IEC/IRB annually or more frequently, if requested. During the pre-study activities, the investigators should have obtained a working knowledge of the regulatory requirements applicable to the study. In particular, the investigators should be aware of their responsibilities, as described in Chapter 4 of the ICH guideline for GCP and in compliance with other applicable regulatory requirements. All observations and findings should be verifiable. This is particularly important for the credibility of the data collected and to assure that the conclusions are correctly derived from the raw data.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Any or all of the recommendations, requests or documents addressed in the ICH guideline for GCP should be available for an audit. Study sites, facilities and laboratories, as well as data (including source data) and documentation should be available for audits.

6.2 Recruitment and consent

Recruitment will be based on a quick scan for eligibility done by the treating physician. When regarded eligible, patients will be informed about this study and are handed the patient information letter, attached in Appendix B. The investigator is responsible for giving the patient complete verbal and written information about the nature, purpose, possible risks and

benefits of the trial. Eligible patients must be notified that they are free to withdraw from the trial at any time and without any reason, and that withdrawal does not affect their usual clinical care. Patients are given one week time in which they may consider participation. When they decide to participate after this period, and within 30 days, a first visit will be scheduled, at which patients will be asked whether they have understood all information received and an investigator or research nurse will obtain a voluntarily signed informed consent form from the patient. A copy of this form will be handed over to the patient. The informed consent form is attached to the patient information letter, and may be found in Appendix B. The sponsor will keep the original signed informed consent form in the patient notes. The sponsor is responsible for obtaining signed informed consent from a patient before performing any trial related procedures.

6.3 Benefits and risks assessment

Participating in this trial will not expose patients to additional risks. Patients may experience added value from participating, because of the extra clinical care that is associated with the follow up visits during this study.

6.4 Compensation for injury

Each center is responsible for providing liability insurance concerning their patients, which will be in accordance with article 7, subsection 6 of the WMO. The study is granted exemption from the obligation to arrange a special insurance for patients according to the WMO by the Medical Ethics Committee.

7. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

7.1 Curriculum vitae

All investigators and research nurses participating in the study, including those who will sign the eCRFs, will supply CROES or its designee with curriculum vitae.

7.2 The Steering Committee

The Steering Committee consists of one principal investigator from each participating center and has the overall clinical responsibility of the study. This Steering Committee shall be comprised of 11 international members.

Tasks and responsibilities include:

- To create and approve the final protocol
- To co-author protocol amendments whenever necessary
- To support and organize the national logistics in the initiation and conduct of the study
- To monitor progress of study enrolment
- To ensure a scientifically sound and safe conduct of the study
- To review and approve the statistical analysis plan
- To guarantee the integrity of data collection and analyses
- To address and resolve study management problems
- To assist in the analyses and presentation of the results

Data management and data analysis shall be the responsibility of the Steering Committee. Representatives of the CROES council may join the meetings of the Steering Committee.

7.3 Handling and storage of data and documents

The investigator or his/her designee will document all data obtained during the study on the individual eCRFs provided by CROES. Investigators will have access to the DMS, and will receive their own username and password. Only data from their own center is accessible to investigators. Data managers from the CROES will have full access to all data collected during this trial, for purposes of monitoring and analyzing the data. The electronic database will be maintained at the central data collection site selected by the CROES council and shall be updated on a regular basis as determined by the CROES council. A manager, selected by the CROES council, at the central data collection site will maintain and coordinate the data collection. As determined by the CROES council, all PIs will receive feedback on the data collection regularly. This also applies to information on patients who underwent baseline examinations required for inclusion to the trial, but who were not included in the study.

Patient data will be entered anonymous, the key to coded information is held at each study center for its own patients and is the responsibility of the local PI. All requested information

must be entered into the electronic case report form and on datasheets or in the medical records. Data entered into the DMS is fully encrypted and therefore anonymized for all participants. Subjects are to be identified by subject number, birth year and center number. Any correction in datasheets should be made by striking through the incorrect entry with a single line and then entering the correct value adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction. The completed eCRF must be signed or authorized by the investigator. The investigator will retain source documents for 15 years in a location which is secure and to which access can be gained if required. The following documents will be archived: investigator file, CRFs and medical records. Handling of personal data is in compliance with the Dutch Personal Data Protection Act.

The number of centers participating in this trial is limited, and participating centers have been selected. These centers must receive approval of the CROES council before commencing the trial. Prior to receiving approval of the CROES council, an IRB approval shall be provided to the central data collection center. Subject to the approval of the CROES council, the PI at study sites should preferably be a member of the Endourological Society.

Primarily, data belongs to the CROES in its function as an organ of the Endourological Society. After a request to the Steering Committee and receiving authorization from the CROES council, study participant members can present data at relevant occasions.

7.4 Monitoring and Quality Assurance

Data managers at the CROES office will assure quality of the data of this trial. All data entered into the web-based data management system will be secured and checked for irregularities. In addition, the DMS provides detailed overview reports of inclusion and runs queries to check for inconsistencies in collected data, to ensure a reliable dataset. To minimize missing data, regular messages will be sent to investigators to encourage and remind them of entering data collected at follow up visits. In each country, and in compliance with good clinical practice (GCP), there will also be an independent monitor when required. This will be the responsibility of the local PIs.

During the trial or after the trial has been completed, the Steering Committee and/or CROES representatives may carry out an audit. The audit will focus on data source verification and critical values in the database. Regulatory bodies may also inspect the study. If a regulatory

authority contacts an investigator with a request for an inspection, the investigator must inform CROES immediately.

7.5 Amendments

Amendments are changes made to the research protocol after a favourable opinion by the accredited MEC has been given. All substantial amendments will be notified to the MEC that gave a favourable opinion and to the competent authority. When the change or deviation will eliminate or reduce the risk to human patients, the amendment may be implemented by the investigator/sponsor before a favourable opinion has been given. In such cases, the sponsor shall notify the MEC of the change or deviation in writing within 10 working days after implementation, and submit the protocol amendment as soon as possible for review. Non-substantial amendments will not be notified to the accredited MEC and the competent authority, but will be recorded and filed by the sponsor.

7.6 Annual progress report

The sponsor/investigator will submit, once a year throughout the clinical trial, a summary of the progress of the trial to the accredited MEC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events / serious adverse reactions, other problems, and amendments.

7.7 End of study report

The investigator will notify the accredited MEC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited MEC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited MEC.

7.8 Public disclosure and publication policy

The Steering Committee will revise and give final approval to any paper derived from the data collected in the course of the study. A list of all participant members and centers will be

included in any publication derived from this data collection. Based on contribution and level of input, the Steering Committee will determine the author names and order of those authors on any paper derived from this dataset.

7.9 Responsibilities of stakeholders

The Principal Investigator is the designated person responsible for the supervision of the study on site. The PI ensures that the study is running on site according to the protocol guidelines and coordinates the data collection and data entry. The PI is responsible for the validity and accuracy of any data entered in the DMS. In case of an audit, the PI is responsible for providing the Audit Committee with source data and is required to assist the work of the said Committee itself. Each center has to appoint an independent physician as patients are entitled to ask questions not only before, but also during and after the study. This physician should not have any association with the study if working in the same institution.

The CROES is responsible for the online DMS, for its set-up and maintenance. The CROES overlooks all data and is responsible for the locking of the database and the statistical analyses.

The Clinical Research Office of the Endourological Society is a non-profit organization with the sole goal of stimulating, conducting, and coordinating the research activities of the Endourological Society. The CROES is not a contract research organization (CRO) or a pharmaceutical or para-pharmaceutical company. The CROES' clinical studies are supported by industry. Financial aid is solely used to support the office's activities and is not used to generate profit. The subsidising party has no influence on the data collection, the data analyses, or the final results. Data collected belongs to CROES and not to the subsidising party. There is no financial support offered to PIs, who contribute to the studies on a voluntary basis. The mission of CROES is to gather data worldwide in order to improve our knowledge and eventually improve the healthcare system.

8. STRUCTURED RISK ANALYSIS

8.1 Potential issues of concern

a. Analysis of potential effect

Patients in the experimental arm (SPIES) will experience no additional risk compared with patients in the control arm (WLI). The control arm consists of patients receiving standard care, and AEs are not commonly reported.

b. Study population

The study population consists of patients with NMIBC who are scheduled for TURB. The condition that these patients are in when entering the study is stable.

8.2 Synthesis

Patients will experience no additional risk when participating in this study.

9. REFERENCES

Reference List

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Cauberg, E. C., Kloen, S., Visser, M., de la Rosette, J. J., Babjuk, M., Soukup, V. et al. (2010). Narrow band imaging cystoscopy improves the detection of non-muscle-invasive bladder cancer. *Urology*, 76, 658-663.

Mowatt, G., N'Dow, J., Vale, L., Nabi, G., Boachie, C., Cook, J. A. et al. (2011). Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis. *International Journal of Technology Assessment in Health Care*, 27, 3-10.

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Sylvester, R. J., van der Meijden, A. P., Oosterlinck, W., Witjes, J. A., Bouffoux, C., Denis, L. et al. (2006). Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur.Urol.*, 49, 466-5.

Appendices

Appendix A – Bladder diagram

Appendix B – Patient Information Form and Informed Consent