



THE GLOBAL RANDOMIZED NBI BLADDER CANCER STUDY

A Multi- Centre, International study to compare use of Narrow Band Imaging (NBI) versus White light (WL) during TURB to assess recurrence of bladder cancer in terms of safety and efficacy

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Clinical Trial Protocol

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A Multi- Centre, International study to compare use of Narrow Band Imaging (NBI) versus White light (WL) during TURB to assess recurrence of bladder cancer in terms of safety and efficacy

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CONFIDENTIALITY STATEMENT

I agree to perform this trial, to maintain the procedures required to carry it out and to abide by the terms of this protocol. This clinical trial protocol is confidential and the property of CROES and may not be used, disclosed or published without their consent.

Investigator Signature

Name:.....

Sign:.....

Date:.....

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1. INTRODUCTION AND BACKGROUND

Urothelial carcinoma (UC) develops in the bladder and the upper urinary tract (UUT), including ureter and renal pelvis. Non-muscle invasive bladder cancer (NMIBC) includes stages Ta, T1 or carcinoma in situ and accounts for $\frac{3}{4}$ of newly diagnosed bladder tumours. In general, UC of the bladder is a multifocal disease with an exceptional high recurrence rate depending on stage and grade of the tumour, necessitating extensive diagnostic and surveillance strategies. The probability of recurrence and progression of NMIBC has been estimated in a pooled analysis of 7 randomized trials of the EORTC. It ranged from 15% to 61% and from less than 1% to 17%, respectively at one year and from 31% to 78% and from less than 1% to 45% at five years. Many factors, such as stage, grade, number of tumours and prior recurrence rate are recognized to influence recurrence with similar hazard ratios, whereas progression is mainly influenced by the grade and the presence of concomitant Cis and a flat lesion (1).

The standard in diagnostics of UC of the bladder is the visual approach including the need for biopsies or transurethral resection. These invasive procedures provide good results for bladder tumours (cystoscopy and transurethral biopsies/resection). Although most of the bladder tumours can be identified with white light cystoscopy, it has been shown that especially in high-grade tumours areas of carcinoma in situ are missed (2). And in case of a positive urinary cytology without visual abnormalities, so-called random biopsies have to be taken to demonstrate the presence of carcinoma in situ. Undetected tumours can later appear as a recurrence, and some might become invasive, highlighting the need to develop alternative endoscopic methods to detect bladder lesions more accurately. A more complete identification may at the very least render the bladder more receptive to successful intravesical therapy (3), and more importantly, may allow for greater detection of high grade/stage tumours, which may alter treatment decisions (4).

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" tumours, and to target biopsies in case of a positive cytology only. This

translates in more complete resection, reducing the recurrence rate of non-invasive tumours (5) and in more appropriate treatments (6).

Another new development in imaging is the narrow band cystoscopy. This technique has been developed by Olympus and is now ready for clinical evaluation in Urology. Narrow Band Imaging (NBI) is a high-resolution endoscopic technique that enhances the fine structure of the mucosal surface without the use of dyes. NBI is based upon the phenomenon that the depth of light penetration depends on its wavelength; the longer the wavelength, the deeper the penetration. Blue light penetrates only superficially, whereas red light penetrates into the deeper layers. The first prototype NBI system (Olympus Corp, Tokyo, Japan) is based upon a light source with sequential red, green, and blue (RGB) illumination. NBI has been investigated in several gastro-intestinal diseases and this technique has shown to be beneficial [7]. In Urology there is limited experience for the role of NBI in detecting bladder cancer but early results are promising [8-11]. However, NBI may have most utility in the operating theatre where a more thorough primary tumour resection may be achievable, as well as reducing the number of tumours that are missed. This could impact the subsequent recurrence rate, resulting in patients experiencing fewer cystoscopic/biopsies/TUR procedures during their disease course, and ultimately leading to a better quality of life and a reduction in the cost of their care.

2. Objectives of the Trial

2.1 Primary study objective

To compare the recurrence rate at 1 year following Narrow Band Imaging and TURB (Arm A) with White Light Trans Urethral Resection of Bladder cancer (TURB) (Arm B) in patients with non muscle invasive (NMIBC Ta/T1) bladder cancer.

2.2 Secondary study objective

- To assess the recurrence of tumour at first follow up (3 months) after Narrow Band Imaging and TURB or White Light TURB in patients with NMIBC.
- To assess the peri-operative morbidity (30 days) of TURB between NBI and WL resection by using the Clavien score
- To define risk factors for the development of peri-operative morbidity after instrumental treatment.
- To assess the recurrence rate related to the surgeon performing the procedure
- To assess the recurrence rate related to additional treatment following TURB.

3. Investigational trial design

3.1 Design

This study is a randomized multi-center study to compare the safety (morbidity) and efficacy between NBI assisted TURB and WL assisted TURB. Each participating center must submit the protocol to their local MEC and each participating centre is responsible for the insurance of their patients. The Academical Medical Center in Netherlands is only responsible for the patients that are treated in their hospital. Data from all participating centers will be collected through online eCFR. All analyses will be performed by CROES members.

3.2 Study Endpoint

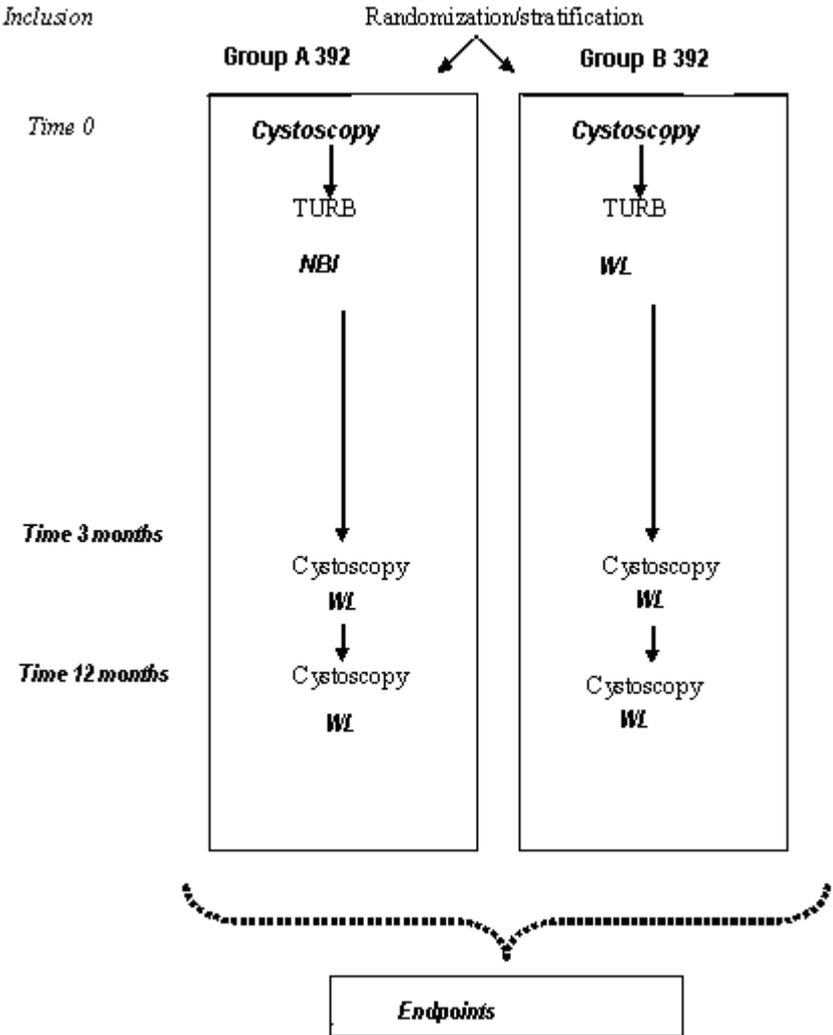
- All lesions must be histological confirmed.
- The proportion of subjects with histology-confirmed tumours (Ta or T1) who have at least one such tumour found by NBI but not by white light cystoscopy.
- Comparison of the proportions of Group A and Group B subjects who undergo TURB for a histology-confirmed Ta or T1 tumour who have a recurrence (histology-confirmed Ta or T1) found at either three or twelve months.

3.3 Randomization and blinding

Patients scheduled for a transurethral resection of a primary bladder cancer with confirmed (multiple) bladder tumour(s) or 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 will be randomized, in a ratio of 1:1, to either arm A (NBI assisted TURB) or arm B (WL assisted TURB).

Randomization is by country using permuted block. Randomization will be utilized by the study center to minimize systematic error and potential selection bias by the investigators. The randomization will be stratified for multiplicity (single or multiple tumors) and macroscopic findings (papillary or solid/flat tumor) according to the finding at work up.

3.4 Study flow chart



3.5 Surgery procedure

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

1. Turn on the white light. Inspection of the bladder and indicating all tumours.
2. If the patient is not randomized to undergo NBI, the patient will be treated according to normal hospital routines. If the patient is randomized to continue with NBI, the following steps will be done:

3. Turn to the NBI. Inspection of the bladder and indicating all papillary lesions and flat and suspicious lesions seen under NBI on a bladder diagram.
4. Perform complete resection (TURB) of all papillary lesions, and obtain biopsies of all flat lesions.

The patients who are randomized to Group B, to have their cystoscopy and TURB with white light will follow the following procedure:

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

Perform resection (TURB) of all papillary lesions and obtain biopsies of all flat lesions/suspicious areas seen. All positive or suspect areas will be resected/biopsied using WL or NBI technique.

3.6 Diagnosis and treatment

All patients in Group A will be treated with NBI and all patients in Group B will be treated with WL. The urologist performing the follow up must preferably be different from the one performing the TURB. Patients will be followed during hospital stay, after 3 and 12 months at a minimum depending on stage and grade of tumours. The whole procedure will be recorded. At three months follow up patients will undergo WL cystoscopy and possible recurrence will be searched for and need histological confirmation. The study is designed to disclose a reduced recurrence rate at 1 year (estimated 10%) in the group treated by NBI TURB compared to the control group, treated by WL TURB.

3.7 Biopsies and histology

Biopsies will be obtained from all flat lesions and suspicious areas and tissue from resected lesions will be collected for histology. Registration of lesions on the bladder chart will include presence of lesion, type (papillary, or flat), number of lesions and location (bladder neck anterior, trigone, around ureteric orifice right, around ureteric orifice left, posterior floor, right lateral wall, cranial wall, left lateral wall, dome, anterior bladder wall and bladder neck posterior). Both biopsied tissue and the histology samples from the resected lesions will be examined by the local pathologist

3.8 Safety assessments

An independent data and safety monitoring board will monitor the patient's safety during the study and give recommendations to the steering committee. This committee has the responsibility to provide the steering committee with recommendations related to the protection of the patients' safety, including stopping recruitment and study treatment. Adverse events will be assessed for seven days after the initial TURB procedure or until resolution. Adverse events will also be recorded at the three and twelve months follow up examinations or until resolved. Vital signs will be measured and a limited physical examination will be performed before the cystoscopy and at hospital discharge, or at the latest 24 hours after the initial TURB/biopsy.

3.9 Study duration

The study consists of a screening evaluation followed by cystoscopy/TURB/biopsies and two follow up cystoscopic examinations at three and twelve months after the initial cystoscopy/TURB/biopsy at least depending on stage and grade of the tumour(s). Since it is not always possible to schedule the follow up visits at exactly three and twelve months, a window of plus/minus two weeks will be accepted. However, after new insights, the Steering Committee recommends a follow up period of 60 months.

3.10 Expected recruitment time

At least 30 centres will be involved in the study. Since the mean follow-up period is expected to be 12 months and each centre is expected to enrol around 30 patients / year, the estimated total duration of the study is two years and six months. Therefore, 30 centres are strictly needed; however as a spare for inactive centres, we will aim for 30-40 centres.

3.11 Source Data Identification

Patient information collected in the eCRF, but not recorded in the patient notes, is regarded as source data. However, data such as visit dates, safety data including AEs and serious adverse events (SAEs), and patients withdrawing their consent as well as information that no study procedures were performed prior to obtaining informed consent should always be recorded in the patient notes and in the eCRFs. The patient notes should also state that the patient is participating in this clinical trial and include a copy of the signed informed consent form. In addition, a copy of the biopsy report from the local pathologist(s) will be filed in the eCRF.

4. Patient selection

4.1 Number of patients and target population

Patients with initial papillary bladder cancer will be included in the study. Expected recurrence rate in the WL assisted TURB is set to 45%. The required sample size per arm is calculated to be 392 patients (784 patients in total). Patients fulfilling the inclusion criteria will be informed about the possibility of participation in this study.

Before any trial related procedures are performed, the patient must be informed, both verbally and in writing; about the study and he/she will be given the opportunity to ask questions. The patient will then sign and date the informed consent form (see **Appendix A** for example patient information with consent form).

4.2 Inclusion criteria

- Signed informed consent
- Patients scheduled for treatment of a primary NMIBC
- Patients should be aged 18 years or older
- No tumours in the upper urinary tract
- No previous irradiation of the pelvis

4.3 Exclusion criteria

- Gross hematuria at the time of TURB. (Note: Gross hematuria is defined as a 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.
- Pregnant (all women of child-bearing potential must document a negative serum or urine pregnancy test at screening and use the contraceptive pill or intrauterine device (IUD) during the treatments and for at least one month thereafter).
- Conditions associated with a risk of poor protocol compliance

4.4 Patient withdrawal

Completion or trial termination for any reason will be fully documented in the eCRF page.

Patients are free to withdraw from the trial at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason for withdrawal may include, but is not restricted to, withdrawal of consent, adverse event(s) or loss to follow up.

5. Treatment procedure

5.1 Diagnosis and Pre-treatment Evaluation

Pre-treatment evaluation at Visit 1 will only be performed after the patient has agreed to participate, has signed and dated the informed consent form. No treatment will be initiated before the informed consent has been given. Stop with anti-coagulation medication before surgery according to the protocol of the hospital.

Pre-treatment evaluation will be performed according to the inclusion and exclusion criteria, including:

- Patient informed consent
- Demographics
- Medical history
- Urinalysis (and culture)
- Urine cytology
- Upper tract imaging

The Investigator/study nurse will complete a screening log of all patients who were approached to enter the trial by entering the patient initials, date of birth and visit date. If the patient then fails to enter the study, the reason(s) for the non-eligibility will be documented.

5.2 Treatment (Visit 2)

Following successful completion of the pre-treatment evaluations, patients will continue into Visit 2. Visit 2 should take place within 14 days after Visit 1 and can be combined with Visit 1.

The following examinations will be performed at Visit 2:

- Limited physical examination
- Vital signs
- Assessment of bladder symptoms prior to TUR/biopsy
- Concomitant medication

5.3 Three month follow up visit 3

All patients will have a routine follow up cystoscopy. A two week window will be allowed for the timing of this examination. All visible lesions should be histologically confirmed. Adverse events will also be recorded.

5.4 Twelve month follow up visit

All patients will have a follow up cystoscopy. A two week window will be allowed for the timing of this examination. All visible lesions should be histologically confirmed. Adverse events will also be recorded.

5.5 Concomitant medication and patient compliance

Any licensed concomitant medication required for the well being of the patient is permitted. Concomitant medication usage will be documented at Visit 1 and during the study.

5.6 Assessment of efficacy

- a)Duration of hospital stay (days or hours)
- b)Duration of operation (minutes)

5.7 Assessment of safety

Safety will be determined by assessment of adverse events, vital signs, and limited physical examination.

Bladder perforation during surgery:

- Using bipolar or monopolar for TURB
- Surgeon related

6. Statistical evaluation and analysis

6.1 Hypothesis to be tested

The endpoints will be analysed by testing the following hypothesis in a sequential order.

1. The proportion of group A and group B subjects who have a recurrence of bladder cancer found at either three or twelve months will be tested. A two-tailed test will be used to test the following null hypothesis:

H_0 : There is an equal proportion of subjects in group A and in group B with recurrence of bladder cancer found at either 3 or 12 months, i.e. $\pi_H = \pi_S$

versus:

H_1 : The proportion $\pi_H \neq \pi_S$.

6.2 Justification of sample size

Sample size calculation is based on the normal approximation to the binomial distribution based on the following specifications:

- a. Randomization rate = 1:1
- b. Clinically relevant difference in recurrence detection rates $\geq 10\%$
- c. Significance level (α -two sided) = 5%
- d. Power ($1-\beta$) = 80%

Expected recurrence rate in the WL assisted TURB is to 35%. The required sample size per arm is calculated to be 392 patients (784 patients in total) To allow for non-compliance rate of 20%, assuming no crossover and no differential loss to follow up between arms, the calculated sample size is inflated by the respective proportion yielding a total of 980 patients.

6.3 Statistical analysis

All analyses will be performed using SPSS 11.5 or higher.

Analysis will be based on the principle of intention-to-treat. All patients who sign the informed consent form, meet the study entry criteria undergo randomization and the procedure will be included in the analysis.

The results will be presented in tables with number of patients (n), mean, standard deviation (std), minimum (min) and maximum (max) for continuous data and with frequencies and percentages for categorical data.

An exact test for single proportion, using the cumulative binominal distribution, with a significance level of 5% (two-sided) will be used for the endpoint, proportion of group A subjects who have at least one papillary lesion found by NBI but not by WL cystoscopy. The proportion will be presented as a total and by center.

Given the possible influence of technology used, the influence of the surgeon performing treatment and additional treatment a multivariate analysis will be performed. Interim analysis will be done after one year for the safety and the short term efficacy by the principal investigator. Safety will be evaluated by the DSMB, which will give regular recommendation to the Steering Committee.

6.4 Handling of missing and spurious data

In the primary analyses of recurrence, missing data at three months will be substituted by the value "recurrence", unless the result at 12 months is "Not recurrence". Missing data at 12 months will be substituted by the value "recurrence".

7. Data management

The Investigator or his/her designee will document all data obtained during the study on the individual eCRFs provided by CROES. 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. The members of the study group will receive feedback on the data collected on a regular basis, as determined by the CROES council

This also applies to data for those patients who, after having consented to participate, underwent baseline examinations required for inclusion into the trial, but who were not included in the study.

There is no minimum or maximum of number of sites participating in this study, however, all sites must receive prior approval of the CROES council.

Subject to the approval of the CROES council, the lead investigator at study sites should preferably be a member of the Endourological Society and in good standing. Subject to the approval of the CROES council, study sites may be proposed by the members from the Steering committee or on recommendation from a third party.

Prior to approval of the site by the CROES council, for quality assurance, an IRB approval will be provided to the central data collection centre.

The data analysis shall be the responsibility of the Steering committee for the study group.

The Steering committee shall be comprised of 11 international members including a chairman. A good balance among the different treatment specialists is desirable. Representatives of the CROES council may be joining during the Steering committee meetings.

7.1 Patient data protection

Data sent to the CROES is fully encrypted and therefore patient anonymized for all participants. Subjects are to be identified by subject number, birth date and centre number. All requested information must be entered on the Electronic Case Report Form in the spaces provided and on datasheets or in the medical record. If an item is not available or is not applicable, it should be documented as such. Any correction in datasheets should be made by striking through the incorrect entry with a single line and then entering the correct answer adjacent to the incorrect entry. The correction must be initialled and dated by the person making the correction. The completed CRF must be signed/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, Case report Forms (datasheets) and Medical records.

7.2 Data handling

Primarily data belongs to the CROES in its function as organ of the Society of Endourology. Eventually, the study participant members can present data after a request to the Steering Committee and authorization from the CROES Council.

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 centres will be included in any publication derived from this data collection. However the name and order of the main authors of any of the papers derived from this data collection will be decided by the Steering Committee of the NBI-Bladder cancer study according to their level of input and contribution and subsequent approval by CROES council.

8. Administrative procedures

8.1 Curriculum vitae

All investigators and study nurses participating in the study, including those who will sign the eCRFs will supply CROES or its designee with curricula vitae (CVs).

8.2 The steering committee

The steering committee consists of one principal investigator from each participating country and has the overall clinical responsibility of the study.

The tasks and responsibilities are:

- To create and approve the final protocol
- To co-author protocol amendments whenever necessary
- To select the investigators network
- To support and organize the national logistics in the initiation and conduct of the study
- To monitor progress of study enrollment
- To ensure a scientifically sound and safe conduct of the study
- To decide on the DSMB recommendations
- To review and approve the statistical analysis plan
- To guarantee the integrity of data collection and analyses
- To address/resolve study management problem
- To assist in the analysis and presentation of the results

8.3 Insurance and liability

The Academic Medical Center is only responsible for the patients that undergo the procedure at the Academic Medical Center. University of Amsterdam has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurer for this trial is: Centramed B.A. Address: Postbus 191, 2270 AD Voorburg

The insurance offers a maximum coverage of:

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

A number of exceptions do exist. The insurance does not cover:

- Damage that based on the characteristics of the trial would have definitely or nearly definitely occurred.
- Damage to the health that would have occurred even if you would not have taken part into this trial.
- Damage as a result of not following the guidelines and instructions.
- Damage to descendants, as the result of a harmful impact of the trial on you and your descendants.
- For research on existing treatment methods; damage as the result of one of these methods.
- For research on treatment of specific health problems; damage as the result of no improvement or worsening of these health problems.

8.4 Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.5 Adverse and serious adverse events

All serious adverse events have to be reported to the coordinating researchers within 24 hours, by fax or email via a specific designed form. The coordinating researchers will then report to the DSMB once every half year.

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;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

8.6 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information. Because of the long experience with NBI and WL, the occurrence of SUSAR's is not very likely. The coordinating investigators will report expedited SUSARs that have arisen in the clinical trial that was assessed by the METC. Also, the coordinating investigators will report all SUSARs expedited to the competent authority, the Medicine

Evaluation Board and the competent authorities in other Member States. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.7 Annual safety report

In addition to the expedited reporting of SUSARs, the CROES office manager will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;

8.8 Follow-up of serious adverse events

All serious adverse events 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.

8.9 Amendments to the protocol

Any change to the study should be written and filed as an amendment to this protocol. The investigator shall submit the protocol amendment for review by the IEC/IRB (and Regulatory Authorities, if applicable) if the change or deviation could increase the risk to human patients in the clinical study, or could adversely affect the validity of the investigation or the rights of the human patients, and shall obtain the approval/favorable opinion of the IEC/IRB and, if applicable to a specific country, Regulatory Authorities before such change or deviation is implemented. When the change or deviation will eliminate or reduce the risk to human patients, the amendment may be implemented by the investigator before

approval/favorable opinion by the IEC/IRB (and Regulatory Authorities, if applicable). In such cases, the investigator shall notify the IEC/IRB of the change or deviation in writing within 10 working days after implementation, and submit the protocol amendment as soon as possible for approval/favorable opinion.

8.10 Ethical principles and regulatory standards

This study will be conducted in compliance with the current revision of the Declaration of Helsinki, ICH guidelines for Good Clinical Practice (GCP) and applicable local regulatory requirements. This includes subject informed consent, investigator reporting requirements and IEC/IRB review and approval. A recognized IEC/IRB must approve this study; IEC/IRB 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 data 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 all data (including source data), and documentation should be available for audits.

8.11 Patient Informed Consent

The Investigator is responsible for giving the patient complete verbal and written information about the nature, purpose, possible risks and benefits of the trial. Trial patients must also be notified that they are free to withdraw from the trial at any time without affecting their usual clinical care. The patients should have reasonable time to read and digest the information before signing. The Investigator is responsible for obtaining signed informed consent from all patients before performing any trial related procedures. A copy of the Patient Information with the Informed Consent Form will be given to the patients. A sample Patient Information with the Informed Consent Form can be found in **Appendix A**. The signed informed consent form will be kept by the Investigator in the patient notes

8.12 Trial Audits and Inspection

During the trial, or after the trial has been completed, Steering committee and/ or Croes representatives may wish to carry out an audit. Regulatory bodies may also inspect the study. If the Investigator is contacted by a regulatory authority with a request for an inspection, the Investigator must inform CROES immediately.

9. References

1. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffoux C, Denis L, Newling DW, Kurth K. 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* 2006;49(3):466-5
2. Loidl W, Schmidbauer J, Susani M, Marberger M. Flexible cystoscopy assisted by hexaminolevulinate induced fluorescence: a new approach for bladder cancer detection and surveillance? *Eur Urol* 2005;47(3):323-6
3. Herr HW. Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette-Guerin therapy. *J Urol* 2005;174(5):2134-7.
4. Herr HW, Donat SM. A restaging transurethral resection predicts early progression of superficial bladder cancer. *BJU Int* 2006;97(6):1194-8
5. Denzinger S, Burger M, Walter B, Kneuchel R, Roessler W, Wieland WF, Filbeck T. Clinically relevant reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid induced fluorescence diagnosis: 8 year results of prospective randomized study. *Urology* 2007;69(4):675-9
6. Jocham D, Witjes F, Wagner S, Zeylemaker B, van Moorselaar J, Grimm MO, Muschter R, Popken G, Konig F, Knuchel R, Kurth KH. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol* 2005;174(3):862-6
7. Lambert R, Kuznetsov K, Rey JF. Narrow-band imaging in digestive endoscopy. *ScientificWorld Journal*. 30:449-65, 2007
8. Bryan RT, Billingham LJ, Wallace DM. Narrow-band imaging flexible cystoscopy in the detection of recurrent urothelial cancer of the bladder. *BJU Int* 2008; 101:702-5
9. Herr HW and Donat SM. A comparison of white-light cystoscopy and narrow-band imaging cystoscopy to detect bladder tumour recurrences. *BJU Int* 2008; 102:1111-4
10. Naselli A, Introini C, Bertolotto F, Spina B, Puppo P. Narrow band imaging for detecting residual/recurrent cancerous tissue during second transurethral resection of newly diagnosed non-muscle-invasive high-grade bladder cancer. *BJU Int* 2009, in press
11. Cauberg ECC, Kloen S, Visser M, de la Rosette JJMCH, Babjuk M, Soukup V, Pesl M, Duskova J, de Reijke TM. Narrow Band Imaging cystoscopy improves the detection of non-muscle invasive bladder cancer. *Urology* 2010 in press

LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
CIS	Carcinoma in situ
CRF	Case Report Form
CV	Curriculum vitae
EC	Ethics Committee
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
ICH	International Conference of Harmonisation
IRB	Institutional Review Board
N.A.	Not applicable
N.D.	Not done
SAE	Serious adverse event
SDV	Source data verification
WL	White light cystoscopy
TURB	Transurethral resection of bladder
WHO	World Health Organization

10. Appendix A Patient Information Sheet, English and Dutch version

Patient Information Sheet

Protocolnummer: NBI 072010

You are being asked whether you want to participate in a research study. Before you decide if you want to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your doctor. Your doctor will spend time explaining the study to you. Please ask your doctor of the study if there is anything that is not clear, or if you would like more information. If you are currently participating in any other study, you cannot take part in this study. Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not.

If you decide not to take part or to withdraw from the study at any time your future medical care will not be affected in any way.

If you decide to take part, you will be asked to sign a consent form and you will be given a signed copy of the consent form and this information sheet to keep.

Study Title:

THE GLOBAL RANDOMIZED NBI BLADDER CANCER STUDY

A Multi- Centre, International study to compare use of Narrow Band Imaging (NBI) versus White light(WL) during TURB to assess recurrence of bladder cancer in terms of safety and efficacy

Purpose of the study

You are approached for this research because you probably have bladder cancer. It is the first time the disease has been diagnosed for you. Your doctor has discussed with you that it is necessary to remove this tumour. The purpose of this study is to investigate further the value of Narrow Band Imaging (NBI) cystoscopy during surgery compared with white light cystoscopy (WL). White light cystoscopy is currently a standard procedure for removing bladder cancers. Narrow Band Imaging (NBI) is a new endoscopic technique using a special light filter resulting in a high contrast resolution of the mucosa and small vascular structures increases. For this technique, special instruments were developed, with the push on a button during the operation the surgeon can change from WL to NBI. This could provide better sight of the bladder cancer during the surgery. If you see the cancer better, the surgery can be performed better. In this study our aim is to analyze if NBI is indeed better to detect and remove all tumours and if this will decrease the likelihood that cancer will return. The procedure will be used during surgery (TURB) and at 3 and 12 months after the removal of your bladder cancer. Additional follow-up cystoscopies at 6 and 9 months could be scheduled depending on the stage and grade of the tumour that was resected.

General information

Withdrawal from the study

Sometimes during the course of a research study new information becomes available about the procedure that is being studied. If this happens, your doctor will tell you about it in a timely manner and discuss with you whether you want to continue in the study. Your doctor may remove you from the study at any time, if he/she does not consider it to be in your best interest to continue.

This may occur if:

- If you fail to follow the instruction of the doctor
- If you experience a study- related injury

You can also withdraw from this study at any time without any consequences. This means that there will be no penalty or loss of medical benefits to which you are entitled and your future care will not be affected

Treatment and Compensation For injury from this study

A standard insurance policy, according to the regulations of the hospital has been organized. This insurance policy covers damage that occurs as a result of death or injury that arises from participation in this trial and which becomes apparent during the course of participation in this trial. The damage is deemed to have become apparent once it has been reported to the insurer.

In the event of a claim you can contact the body responsible for setting claims:

Confidentiality and Data Protection

By signing this form you consent to the doctor and his or her staff collecting, processing electronically and sign your personal data for the study. This includes: your date of birth, your sex, your ethnic origin and personal data on you physical or mental health or condition.

Your consent to your doctor does not have a specific expiration date, but you may withdraw your consent at any time by notifying the doctor.

The study data is protected by the use of a code, which is a number specific to you. The doctor is in control of the code key, which is needed to connect your study data to you.

Whom to ask if you have questions

An independent Ethics Committee METC has reviewed the study and has given an approval/ favourable opinion for it.

If you have any questions or concerns about the research or your rights as a patient, or any injury or you are unwell, please contact you study doctor or the study coordinator.

Independent Physician

Should you have any further questions after reading this information which you would like to discuss with an independent physician, you can contact Dr. Klump, on 020 566 5957. This physician is not involved in this study, but is informed.

11. Appendix B

Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC 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 METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC 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 METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the procedure or device. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Adverse events occur from the moment that the informed consent form has been signed.

All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Patients will be monitored and questioned at every visit regarding the occurrence and nature of adverse events; symptoms reported by the subject and clinically relevant changes (eg. laboratory) and abnormalities observed by the investigator would be recorded. Adverse events, which are worsening in intensity, become a new adverse event.

The investigator will record all Adverse Events on the Adverse Event Log in the Case Report Form with information about:

The Adverse Event and relevant clinical findings, date of onset, date of recovery, intensity, action taken to treat the event, causal relationship to the procedure, seriousness and (date of) outcome.

Adverse events should be described as diagnoses if available. If not, separate signs and symptoms have to be described.

The following 4-point scale will be used for rating the causal relationship of the adverse event to the procedure:

Definitely not related: clearly due to extraneous causes. Information is contradictory of a causal relationship.

Possibly related: an adverse event that follows a reasonable temporal sequence following the procedure that could have been produced by the subjects clinical state or by other therapies

Definitely related: an adverse event that follows a reasonable temporal sequence following the procedure and is known as to be a complication of the procedure for which no other explanation can be determined

The intensity will be graded as follows: (conform the 5-point scale of the NCI common terminology criteria version 3 for adverse events.

Grade 1 as mild AE; usually transient in nature and not interfering with normal activities. May require additional therapy

Grade 2 as moderate AE sufficiently discomforting to interfere with normal activities and requires intervention or additional therapies;

Grade 3 as severe AE; prevents normal activities and necessitates additional therapy

Grade 4; life-threatening or disabling AE

Grade 5; death related to AE

The outcome will be recorded as:

- Recovering
- Not recovered
- Recovered
- Recovered with sequelae

A serious adverse event includes any of the following events, which may or may not be considered related to the device or procedure;

- Death due to any cause
- Life threatening or permanently disabling events and incapacities
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation to prevent death, life-threatening events or permanently disabling events.
unless the admission results in a hospital stay of less than 12 hours
unless the admission is pre-planned
unless the admission is not associated with an adverse event
- Is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction,

12. Appendix C

Responsibilities of the local Principal Investigator (PI)

The Principal Investigator (PI) 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 the data entry. The Principal Investigator is responsible for the data entered in the CROES Data Management System, for its validity and its accuracy. In case of audit, the Principal Investigator is responsible for providing the Audit Committee with source data and is required to assist the work of the Audit Committee itself.

Responsibilities of the CROES – data management

The CROES is responsible for the online Data Management System (DMS), for its set-up and maintenance (see Par. 7). The CROES overlooks all data and is responsible for the locking of the database and the statistical analysis.

CROES Status

The CROES is the Clinical Research Office of the Endourological Society. The CROES 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 sponsors have no influence on the data collection, the data analysis or the final results. Data collected belongs to CROES and not to the sponsors. There is no financial support offered to principal investigators, 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 healthcare system.