NCT03058705
Pilot Study: Assessing Near Infrared Fluorescence Imaging Medical Technology for the Detection of Bladder Cancer

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(Department of Urology)
1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

Primary Aim
The primary outcome of this study is to determine the minimal dwell time needed for adequate detection of Cysview avid tumors using protoporphyrin IX (PpIX) near infrared fluorescence (NIRF).

Secondary Aim
To determine in vivo the ratio of intensity of near infrared fluorescence (NIRF) signal arising from the tumor compared to that arising from normal tissue as a function of dwell time.

1.2. Background

Bladder cancer is the fifth most commonly diagnosed solid malignancy in the United States, with patients experiencing multifocal occurrences/recurrences even after seemingly successful treatment of non-muscle invading urothelial cancer. There is level 1 evidence that more complete tumor eradication results in patients experiencing fewer recurrences [1, 2]. Bladder cancer is the most costly malignancy to treat over the lifetime of patients in large part because of the need for multiple re-treatments and surgeries as well as lifelong endoscopic surveillance [3]. Thus, a practical way to improve tumor detection and removal will not only benefit individual patients but also should reduce the overall cost of managing this malignancy.

One method that improves the completeness of transurethral resection of bladder tumors (TURBTs) utilizes intravesical administration of the hematoporphyrin derivative Cysview™ (brand name Hexvix™ elsewhere) to detect tumors not readily visualized with standard white light cystoscopy. Tumor lesions are visualized intra-operatively by shining a blue light throughout the bladder that excites the resultant intracellular PpIX to emit red fluorescence; tumor cells exhibit a lower clearing rate of PpIX because of altered catabolism and transport [4-6], thus it accumulates and permits differential visualization.

Standard of care at UR for diagnosis of bladder tumors consists of white light cystoscopy only in office and then in OR where tumor is biopsied or resected. Fluorescence (blue light cystoscopy) is rarely done in large part because it requires preoperative catheter passage and drug (Cysview) instillation for 60 minutes before surgery (causes patient discomfort) and the actual operation is lengthened. While this technique is efficacious, it requires expensive special equipment, a need to examine the bladder under both white to blue light repeatedly during the case, and the solution (Cysview™) must be instilled 60 minutes before the procedure via a catheter. This inconvenient requirement leads to delay and greater expense for the facility as well as prolonging patient discomfort and apprehension. For these reasons, blue light cystoscopy has not been as widely adopted as one might expect given its clear benefits [1, 2].
We hope to eliminate the obstacles to better care by employing new and more sensitive imaging technologies that should enable more rapid tumor identification and a reduction in bladder dwell time. Agent administration could be done in the operating room just minutes before cystoscopy is performed. We will achieve this by using highly sensitive imaging technologies similar to those used in astronomy to detect near infrared fluorescence (NIRF); this imaging system will detect NIRF emitted by PpIX. Note that conventional blue light cystoscopy detects the red fluorescence emitted by PpIX. This enables two significant advances. First, NIRF can be elicited by white light excitation alone, so there is no need to use separate blue light excitation. Second, the white light image can be simultaneously acquired (viewed and/or recorded) with the NIRF image, so there is no need for switching between the blue light and the white light imaging modes as in conventional blue light cystoscopy.

Thus, this new technology will obviate the need for pre-anesthetic urethral catheterization, the hour wait in the pre-anesthetic area. This reduction in dwell time is made possible by the increased sensitivity of NIRF imaging to PpIX fluorescence. We have found ex-vivo the NIRF imaging is well over 10 times more sensitive to Cysview fluorescence than standard blue light cystoscopy. Ex-vivo preliminary studies have shown that blue light cystoscopy can detect PpIX concentrations 1 microgram per milliliter. In contrast, NIRF imaging was able to detect PpIX concentrations down to 0.01 microgram per milliliter, a 100 fold difference (Appendix 4). In addition, as this imaging technology utilizes existing conventional white light cystoscopes, it also averts the requirement for current costly and single purpose blue light generating equipment that cannot be used for other endoscopic procedures.

Many large tumors are readily seen with white light, and we expect to visualize large tumor fluorescence in a few minutes with the new system.

2. STUDY DESIGN

2.1. Overview

The study will be a single center prospective nonrandomized trial of an investigational imaging technology. All patients will undergo investigational imaging and concomitant standard of care transurethral resection of bladder tumor (TURBT). Patients with suspected bladder cancer on cystoscopy will be enrolled to have subsequent intraoperative intravesical administration of Cysview and NIRF cystoscopy immediately prior to TURBT.

2.2. Rationale for Study Design

Although studies have evaluated optimal dwell time for Cysview fluorescence when cystoscopy is performed under blue light, the optimal dwell time for NIRF visualization has not been determined. Prior to conducting randomized studies comparing efficacy of NIRF and blue light we must first establish that a useful and short dwell time can in fact be used successfully. This pilot study will allow us to identify a dwell time for subsequent NIRF cystoscopy studies.
Because from a practical point of view, that is the longest time period we want to prolong surgery with a product that should equal or improve on current blue light cystoscopy. We use blue light very selectively now for these reasons: The Dwell study and the subsequent research that comes from it – should permit avoidance of the pre-op catheterization and significantly shorten the procedure. We have found ex-vivo the NIRF imaging is well over 10 times more sensitive to Cysview florescence and should have no problem with visualization at 10 minutes.

2.3. **Rationale for Dosage**

Intravesical instillation of 100 mg Cysview (hexaminolevulinate hydrochloride) will be performed via foley catheter at the initiation of the procedure. Although NIRF is more sensitive than blue light cystoscopy, we will use the current FDA approved dose. Cysview has a favorable safety profile at this dose.
2.4. **Equipment**

This protocol relies on intravesical administration of an FDA-approved agent for bladder cancer detection (Cysview™) that fluoresces upon illumination with an FDA-approved cystoscopic white light source. Standard light sources emit near-infrared wavelengths that would interfere with detecting NIRF, so the cystoscopy light source is filtered to block these wavelengths and thus improve the signal to noise ratio. A standard (FDA-approved) cystoscope is introduced into the bladder and used to guide resection of any detected tumors, i.e. Trans Urethral Resection of Bladder Tumors (TURBT). Color and near-infrared image streams will be recorded. The surgeon will be able to display white light images, white light images with pseudocolor highlighting the near-infrared fluorescent tumor, a NIRF image, or a combination of images.
3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) Number of Subjects:

We will enroll 20 subjects to get 10 evaluable subjects in the study. It is expected there may be a high withdrawal rate due to the availability of the study team to all be present on the subject’s surgery date.

b) Gender and Age of Subjects:

Male and female patients who are 18 years or older will be included. Cysview is equally efficacious and safe across both sexes. There is no scientific or medical justification to restrict inclusion of the adult population further by age.

c) Racial and Ethnic Origin:

There is no restriction of or subject population based on racial or ethnic grounds.

d) Vulnerable Subjects:

No vulnerable subjects will participate in this study.

3.2. Inclusion and Exclusion Criteria

a) Inclusion Criteria:

• Diagnosis of bladder mass on office cystoscopy suspicious for malignancy, either newly diagnosed or a recurrent tumor
• Planned transurethral resection of bladder tumor in the operating room
• Men or women (age 18 or older)
• Any racial or ethnic origin
• Ability to give informed consent

b) Exclusion Criteria:

• Pregnancy
• Nursing mother
• Diagnosis of porphyria
• Gross hematuria
• BCG immunotherapy or intravesical chemotherapy within the past 90 days
• Known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid
3.3. **Discussion of Subject Population**

The inclusion/exclusion criteria will be representative of the population that would benefit from reduced Cysview dwell time provided by NIRF cystoscopy. Patients will be excluded based upon the known contraindications for Cysview.

4. **SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT**

4.1. **Method of Subject Identification and Recruitment**

Subjects will be identified through eRecord or clinic schedules by the study team and will be recruited from the clinical offices in the Urology Department at the University of Rochester.

4.2. **Process of Consent**

A member of the study team with routine access to all UR Urology patients will identify potential subjects via eRecord or clinic schedules. Once a potential subject is identified and the urologist notified, the study team will introduce the study at a scheduled clinic visit and check for interest in participation. If interested, eligible subjects may be enrolled at this visit. If potential subjects wish to take the consent form home to read and review with family or friends, a member of the study team will call the patient to check their interest in participation and answer any questions they may have about the study. Informed consent will then be obtained by a member of the study team at their pre-operative visit (see Schedule of Activities – Appendix I).

Subjects will be reminded that they can elect not to participate without risking loss of any present they would normally receive. Any questions the subject may have will be answered. A copy of the signed consent form will be given to the subject and the original consent form will be placed in the research record. All research records will be accessed by the study team and stored in a locked office of the study team. Consent will be obtained in a private setting with a closed door to ensure privacy.

5. **METHODS AND STUDY PROCEDURES**

The study will be a single center prospective nonrandomized trial of an investigational imaging technology. All patients will undergo investigational imaging and the concomitant standard of care, i.e. transurethral resection of bladder tumor (TURBT). Patients with suspected bladder cancer on cystoscopy will be enrolled to have subsequent intraoperative intravesical administration of Cysview and NIRF cystoscopy prior to TURBT.

Ten patients will be recruited to demonstrate the feasibility of using this NIRF imaging system at shorter intravesical instillation durations (Cysview™ dwell time). The instillation duration will be 10, 5, or 2.5 minutes in this patient series. The subject will be anesthetized, positioned, prepped, and draped for the white light TURBT. A catheter will be passed, Cysview instilled, and the catheter clamped for the assigned dwell time. It will then be unclamped after the dwell time designated, Cysview will be
allowed to drain out, the catheter removed, and cystoscopy performed. The
cystoscope is inserted and imaging of the entire bladder commences while recording
both color and near-infrared image streams (movies and periodic stills). This initial
survey that includes catheterization of the bladder under anesthesia, instillation of
Cysview, dwell time as indicated and subsequent evaluation with the color and near-
infrared imaging for research purposes. Cysview with blue light cystoscopy has been
indicated to be desirable at the time of TURBT but it is not standard of care; it is an
optional procedure to increase detection and decrease recurrence. A useful dwell time
for Cysview before NIRF imaging will be identified in this study; an effort will be made
to minimize the interval between administration and imaging.

The procedure and all study portions will be performed by the subject’s surgeon.
During the procedure, the bladder will initially be examined in a systematic meridian
fashion. Suspicious tumors identified by white light only, NIRF only, and both will be
identified. If fluorescence is detected in 3/3 subjects at a given dwell time, the study
will continue to shorter dwell times. The initial 3 subjects will have 10 min dwell
duration, followed by 5 min and 2.5 min. If fluorescence is not detected in 3/3 subjects
at any time period, the study will not progress to shorter dwell times. If no
fluorescence is visualized after 10 minutes, we will not proceed to a longer dwell time.

When tumor NIRF is detected, the localized intensity of the fluorescence image will be
quantified by comparing the emission arising from the tumor location to the
background emission from surrounding normal tissue. The ratio of intensity between
the tumor location and the surrounding normal tissue will be used to quantify the signal
strength and provide evidence of comparative sensitivity for dwell times.

When the tumor survey is completed, resection of the identified lesions commences
according to normal standards of care, i.e. TURBT. Random bladder biopsies are
considered standard of care at the time of TURBT. We will take directed biopsies of
areas identified by NIRF imaging and treat these as random bladder biopsies.

All specimens will be handled according to standard of care practice and pathologic
diagnosis conducted by a genitourinary pathologist.

Study medication will be ordered from the UR Pharmacy and distributed by the
Department of Urology at no cost to the subject. Study medication will be stored in a
locked cabinet and only accessed by the study team.

Imagin Medical will pay for the cost of the study medication (Cysview) and consigned
the NIRF imaging equipment for the study.
5.1. **Treatment Dosage and Administration**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pre-medications; Precautions</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
<th>Cycle Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysview</td>
<td>None</td>
<td>100 mg</td>
<td>Bladder instillation by catheter</td>
<td>Intraoperative</td>
<td>10 minutes maximum</td>
</tr>
</tbody>
</table>

5.2. **Efficacy Assessments**

This initial series is designed solely to demonstrate that tumors identifiable under white light will be seen to fluoresce in the near-infrared spectrum after relatively short dwell times. We will document detectability of individual tumors under white light and NIRF at short intervals after Cysview instillation.

5.3. **Safety Assessments**

Standard patient preoperative assessment will be performed including medical history, physical exam, vital signs, pertinent clinical labs and pre-anesthesia evaluation if deemed necessary. No additional procedures specific to this study will be performed for safety assessment.

5.4. **Assessment of Subject Compliance**

There are no subject compliance issues to be monitored.

5.5. **Costs to the Subject**

There will be no cost to the subject. The subject will have no additional research visits. Study medication and the use of the NIRF Imaging equipment will be provided by Imagin Medical.

5.6. **Payment for Participation**

There will be no payment for participation.

5.7. **Return of Individual Research Results**

No research results will be provided to the subject. They will have a discussion of resection pathology with their surgeon post procedure as is standard of care.
6. CONCOMITANT AND DISALLOWED MEDICATIONS

No medications will preclude participation. No medications will need to be stopped for participation, except as needed for anesthesia and to undergo TURBT (eg. anticoagulants).

7. SUBJECT WITHDRAWALS

N/A

8. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

8.1. Study Drug

Cysview™ (hexaminolevulinate HCL)

Study Device

This protocol relies on intravesical administration of an FDA-approved agent for bladder cancer detection (Cysview™) that will fluoresce upon illumination with an FDA-approved cystoscopic light source. This study will use lowered intensities from the light source; near-infrared wavelengths in the spectral region of interest (spectrally overlapping with NIRF signal) that are emitted by a white light source will be removed with a filter to enable detection of the same wavelengths emitted by tumor fluorescence. The imaging system is new.

A standard (FDA-approved) cystoscope that is currently in use in the SMH OR is introduced into the bladder and is used to guide resection of any detected tumors, i.e. Trans Urethral Resection of Bladder Tumors (TURBT). Color and near-infrared image streams will be recorded. The surgeon will be able to display white light images, white light images with pseudocolor highlighting the near-infrared fluorescent tumor, near-infrared image, or any pair of images. Since the NIRF is in a spectrum that is not visible to the human eye, the computer will display this florescence in a color that is in the visible spectrum or pseudo-color.

Our imaging system does not fit the definition of significant risk device study and therefore qualifies as a non-significant risk device study as follows:

- NIRF imaging is not an implant and does not present a potential for serious risk to health, safety or welfare of a subject.
- NIRF imaging is not for use supporting or sustaining human life.
- Although NIRF imaging will be used during cystoscopy, resection and pathologic diagnosis of cancer will occur independently to NIRF imaging.
- There is no potential for serious risk to health, safety or welfare of the subject
8.2. **Dosage of Study Drug/Biologic**

<table>
<thead>
<tr>
<th>REGIMEN DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Cysview</td>
</tr>
</tbody>
</table>

8.3. **Subject Enrollment/Randomization**

Subjects will be assigned a drug dwell duration based upon the order of study entry. No randomization will occur. The first three study subjects will have a 10 minute dwell time. If the dwell time fluorescence is adequate, dwell time will be reduced to 5 minutes for the next three subjects and then 2.5 minutes accordingly.

8.4. **Accountability of Investigational Supplies**

Study medication will be stored in a locked cabinet and only accessed by the study team. Study medication will be distributed intra-operatively directly by the study team. Any returned medication will be documented within the study subject’s research record and disposed of according to the research pharmacy recommendations. The investigational imaging system will be maintained according to operating room standards. The system will be stored in a locked room and only accessed by the study team.
8.5. **Subject Withdrawal of Study Drug**

Subjects who withdraw from the study will not be eligible to re-enroll in the study.

8.6. **Emergency Drug Disclosure**

As this is not a blinded study, emergency drug disclosure does not apply.

9. **SAFETY AND REPORTABLE EVENTS**

9.1. **Adverse Event Definition**

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study intervention.

9.2. **Serious Adverse Event Definition**

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage

9.3. **Recording Adverse Events**

The study staff will assess adverse events by recording all voluntary complaints of the subject post-TURBT (i.e., after Cysview administration in the OR).

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, will be documented on the Adverse Event Summary Log. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, attribution, severity grade, relationship to investigational product (i.e., drug or device), contributing factors, any action taken in response to the study drug/device, and whether the adverse event was expected vs unexpected. The CTCAE (version 4) will be used to assign severity grade of the adverse event.

Adverse events will be documented from the time of Cysview administration until their post-op visit.
9.4. **Responsibilities for Reporting Serious Adverse Events**

All serious adverse events will be documented on the Adverse Event Summary Log and subject’s research chart. The principal investigator will be notified immediately of any serious adverse events, and subsequently, the RSRB while complying with regulations and RSRB policy regarding the reporting of adverse events. Since Cysview has a favorable safety profile, we do not anticipate any SAE’s in this study.

All serious adverse events will be reported to the Wilmot Cancer Institute’s Data Safety Monitoring Committee (DSMC) using the DSMC SAE Review Form. All unexpected and related adverse events will be reported to both the RSRB and to the DSMC within 10 calendar days.

10. **RISK/BENEFIT ASSESSMENT**

10.1. **Potential Risks**

Known adverse effects of hexaminolevulinate administration include: headache or procedural pain (1%-10%), bladder spasms (2%), bladder pain, dysuria, hematuria (<10%). Abnormal urinalysis, cystitis have been reported (<1%). Anaphylaxis and hypersensitivity reaction has occurred (<1%). [7]

There is no increased risk of adverse effects from the use of the NIRF imaging system. All medications and equipment components in contact with the subject are FDA approved for use in this patient group. Clinical engineering electrical safety certification will be performed. Cystoscopic light sources approved for human use will be used, but at reduced near infrared intensity for imaging purposes; thus less energy is introduced into the patient than would normally occur.

10.2. **Protection Against Risks**

To protect subjects from risk, all individuals with hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid will be excluded from participation in this study. The installation time utilized in this study will be 10 minutes as compared with the 60 minute instillation time approved by the FDA, further reducing risk of potential adverse events. Subjects will be hemodynamically monitored by anesthesiologists throughout the instillation which will provide early warning of adverse events if any.

10.3. **Potential Benefits to Subjects**

Blue light cystoscopy with the use of Cysview augments identification of hard to visualize tumors and aids in identifying additional areas requiring tumor resection. The use of Cysview with blue light cystoscopy requires dwell times of 60 minutes that is a logistical challenge. The development of highly sensitive detection equipment may allow a reduction of the Cysview dwell time. The reduction in dwell time may also reduce unintended side effects by reducing the duration of mucosal contact with Cysview.
10.4 Alternatives to Participation

There are no alternatives to participation. This study is voluntary and subjects do not have to participate.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

All subjects will be assigned a unique code number and the key will be kept on a password-protected database in a locked office of the study team. Signed consent forms, case report forms, and data collection sheets will be kept in binders in the locked office of the Clinical Trials Office.

Imaging data will be kept on a secure Information Systems Division private network server within the University of Rochester Medical Center. This data will be password-protected, accessible only by study team members listed on this study. The data will be kept indefinitely. Only the study team will have access to the data.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

Administration of study medication will be documented in the medical record.

13. DATA ANALYSIS AND MONITORING

13.1. Sample Size Determination

Conventional blue light cystoscopy has a sensitivity of better than 0.9 (90%) for Ta-T4 tumors. Therefore, the probability that we will fail to detect the tumors in three subjects due to the sensitivity of the blue light method is less than 0.001 (0.1%). We thus believe that 3 subjects represent a sufficient sample size to determine the efficacy of this method.

13.2. Planned Statistical Analysis

The procedure will be digitally recorded during simultaneous acquisition of the visible (white light) image and the fluorescence image from separate cameras with precisely aligned fields of view. At any time point, both cameras record the image from the same tissue location as relayed by the cystoscope. Therefore, the images are completely spatially coordinated and the location of any feature (tumor) observed on the white light image will be known in the corresponding image recorded by the fluorescence detection camera. Accordingly, tumors visualized by the white light image should be visible in the fluorescence image as features with enhanced emission. This association thus enables us to determine if PPIX emission arising from tumors is detectable within the specified dwell time. The localized intensity of the fluorescence image will be quantified by comparing the emission arising from the tumor location to the background emission from surrounding normal tissue. The ratio
of intensity between the tumor location and the surrounding normal tissue will be used to quantify the signal strength. We will use this value for further analysis to quantify the signal strength as a function of dwell time.

13.3. Data and Safety Monitoring

Study Investigators will conduct continuous review of data and subject safety. The Investigator will submit semi-annual progress reports of these data to the Data Safety Monitoring Committee at the Wilmot Cancer Institute for review. The review will include for each treatment arm/dose level: the number of subjects enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed.

The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the AE spreadsheet along with the Progress Report to the Data Safety Monitoring Committee at the Wilmot Cancer Institute for review. Actual review dates will be assigned when the first subject is accrued.

- Any serious adverse event that is serious, related AND unexpected must be reported within 10 calendar days to both the Safety Coordinator at the Wilmot Cancer Institute and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when subject safety is of concern, an interim meeting may be called.

- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the DSMC for review at the next quarterly meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The Data Safety Monitoring Committee provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk and complexity of the trial, and is assigned by the Protocol Review Committee at the time of their initial review and approval. The Data and Safety Monitoring Committee will monitor all adverse event rates utilizing a cumulative spreadsheet listing of all events submitted along with progress reports by the PI. All serious adverse events that have occurred in the prior 3 months will be reviewed at the regular quarterly meeting of the DSMC in order to confirm toxicity grade, expectedness, relatedness, sequelae, follow up required, and risk to current or future subjects.
14. REFERENCES


http://ac.els-cdn.com/S0022534712030108/1-s2.0-S0022534712030108-main.pdf?_tid=ed4c6b4c-4865-11e6-97be-00000aab0f6c&acdnat=1468351509_fdecabf3754c0ff233fe229ec69b0b9c


http://ac.els-cdn.com/S0022534707005435/1-s2.0-S0022534707005435-main.pdf?_tid=eaa56498-4865-11e6-adb2-00000aab0f27&acdnat=1468351504_ac62489e673091ac976d93ca2d09e5c4


Appendix 1

Schedule of Activities

<table>
<thead>
<tr>
<th>PROCEDURES</th>
<th>Research Visit</th>
<th>Pre-Op Visit</th>
<th>Day of Surgery</th>
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<tbody>
<tr>
<td>Confirm Eligibility</td>
<td>X</td>
<td>X*</td>
<td></td>
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<tr>
<td>Obtain Informed Consent</td>
<td>X</td>
<td>X*</td>
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<tr>
<td>Medical History and Demographics</td>
<td>X</td>
<td></td>
<td>X^</td>
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<tr>
<td>Concomitant Medication Review</td>
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<td>X^</td>
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<tr>
<td>Dispense Study Drug</td>
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<tr>
<td>Near-Infrared Imaging</td>
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<td>X</td>
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<tr>
<td>Adverse Event Review</td>
<td></td>
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<td>X</td>
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</tbody>
</table>

*If not obtained at the Research visit, may be obtained at the Pre-op visit

^If not obtained at the Research visit, may be obtained Day of Surgery
## Appendix 3

### Data Collection Form

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Male or Female</th>
<th>Age</th>
<th>History of Bladder Cancer</th>
<th>Video File</th>
<th>Dwell Time</th>
<th>Adequate Assessment of Florescence</th>
<th>Pathology of Directed Biopsies</th>
<th>Pathology of Primary Specimen</th>
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Appendix 4

Preliminary ex-vivo results: Comparison of sensitivity between imaging modalities

Our method offers at least two orders of magnitude higher sensitivity