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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
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Title of Protocol:
Acupuncture vs. Standard of Care for Induction Intravesical BCG-related Adverse Events in High-Risk Non-Muscle Invasive Bladder Cancer

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Sponsor: Early Phase Clinical Research Support Application, Cancer Center Support Grant
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PROTOCOL SYNOPSIS

Protocol Title	Acupuncture vs. Standard of Care for Induction Intravesical BCG-related Adverse Events in High-Risk Non-Muscle Invasive Bladder Cancer
Protocol Number	RG1007421
Protocol Sponsor	CCSG
Trial Phase	Phase II
Trial Type	Randomized Control Feasibility Trial
Clinical Indication	Nonmuscle-invasive bladder cancer (NMIBC) receiving induction Bacillus Calmette–Guerin (BCG) therapy
Study Objectives	The overall objectives of this proposal are to evaluate the feasibility and impact of weekly acupuncture compared to a no acupunture ("waitlist") control group among patients being treated with BCG for NMIBC. **Primary objective:** To test the feasibility and safety of integrating an outpatient acupuncture protocal prior to weekly BCG instillations into the Urology Clinic workflow. This will be assessed by trial recruitment, retention, protocol adherence, patient/provider feedback and evaluation of adverse events. **Rationale:** This objective will measure the extent to which the study intervention can be successly incorporated into the intravesical induction BCG regimen. Recruitment, retention and adherence is also relevant to inform future power calculations for a Phase III clinical trial. Patient/provider feedback will be used to evaluate how the intervention impacts clinical workflow and burden to assess potential issues that may impact future implementation and the ability to scale up the intervention more broadly. Lastly, this objective will determine the safety and tolerability of adjuvant acupuncture in patients undergoing induction intravesical BCG for NMIBC. **Secondary objectives**: To test whether acupuncture may help patients complete the 6-weekly instillations of intravesical BCG. This will be assessed through a patient's completion of BCG regimen, patient-reported outcomes of urinary symptoms and overall quality of life (as measured by the EORTC QLQ-NMIBC-24(1) and EORTC QLQ-C30(2) scales, respectively) and quantification of medication use for symptom management. **Rationale:** A goal of this study is to identify an adjunctive therapy that can help patients complete the induction BCG through reduction of urinary and pelvic treatment side effects. These data will provide both direct and indirect measures of acupuncture as a potential intervention tool and inform future power calculations for a Phase III clinical trial.
Study Design	Randomized Control Feasibility Trial
Population	45 BCG- adults from the UWMC Department of Urology who are scheduled to receive 6 weekly doses of intravesical BCG. Eligibility criteria includes 1) age 18 years or older, 2) English-speaking, 3) diagnosis of American Urological Association (AUA) high-risk NMIBC, including high grade (HG) pT1 (invading only the lamina propria of the bladder), recurrent HG pTa (superficial tumors), HG pTa >3cm in size or multifocal, any carcinoma in situ, any variant histology, any lymphovascular invasion, and HG prostatic urethral involvement(3) 4) have not received acupuncture in the previous 3 months, and 5) willing and able to participate in trial activities.
Primary Endpoints	1. Feasibilty, as assessed by recruitment, retention, and adherence to the acupuncture protocol. 2. Safety and tolerability of acupuncture protocol (physician reported CTCAE v5.0 adverse events).

Secondary Endpoints	1. BCG treatment adherence, interruptions, dose-reductions, completion of therapy as intended 2. Patient reported urinary symptoms (EORTC QLQ-NMIBC-24) and patient-reported quality of life (EORTC-QLQ-C30) 3. Use of medications for symptom management per patient report and per prescription
Type of control	Waitlist arm – receives no acupuncture prior to BCG
Investigation Drug	N/A
Dose	Acupuncture: 6 weekly treatments with 30 minute needle retention
Route of administration	Acupuncture: filiform needle insertion
Regimen	6 weekly sessions treatments prior to BCG
Trial Blinding	None
Treatment Groups	Arm A: Acupuncture Intervention – Dose given pre-BCG treatment with standard of care symptom management. Arm B: Waitlist Control Arm – No dose given pre-BCG treatment with standard of care symptom management and 4 coupons for acupuncture after study completion.
Treatment Schedule	Once weekly for six weeks
Efficacy Assessments	Baseline Weekly at BCG treatment 1 week following last treatment
Number of trial subjects	45
Estimated duration of trial	12 months
Duration of Participation	Eight weeks

ABBREVIATIONS

NMIBC	Nonmuscle-invasive bladder cancer
BCG	Bacillus Calmette–Guerin
QOL	Quality of life
AUA	American Urological Association
OAB	Overactive bladder
PTNS	Percutaneous Tibial Nerve Stimulation
UWMC	University of Washington Medical Center
HG	High grade
pT1	Invading only the lamina propria of the bladder
HG pTa	Superficial papillary bladder tumors, noninvasive
TCM	Traditional Chinese Medicine
GMP	Good Manufacturing Practices
AAMI	Association for the Advancement of Medical Instrumentation
ISO	International Organization for Standardization
CE Mark	European Conformity Marking
WHO	World Health Organization
EA	Electroacupuncture
FDA	U.S. Food and Drug Administration
NCCAOM	National Certification Commission for Acupuncture and Oriental Medicine
SCCA	Seattle Cancer Care Alliance
BCAN PSN	Bladder Cancer Advocacy Network Patient Survey Network
SOC	Standard of care

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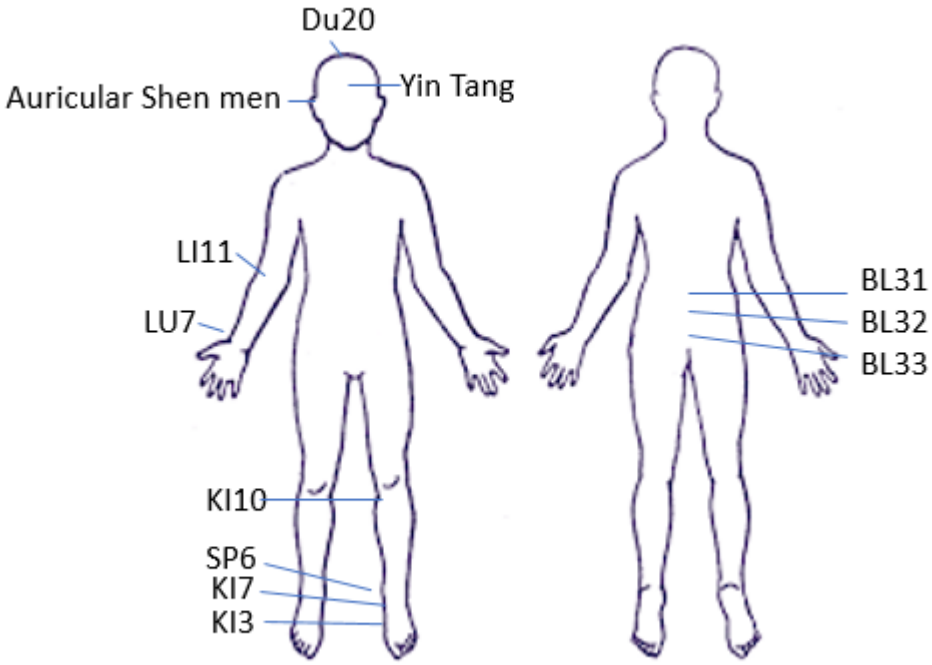

1.0 GENERAL INFORMATION

The standard of care treatment for high-risk nonmuscle-invasive bladder cancer (NMIBC) is 6-weekly instillations of intravesical Bacillus Calmette-Guerin (BCG). However, patients frequently experience treatment interruptions and/or discontinuation due to urinary and pelvic side effects of this treatment. Strategies to minimize BCG-associated toxicity are needed to improve treatment adherence and subsequent NMIBC clinical outcomes. We will evaluate the feasibility and effects of acupuncture compared to a waitlist control on bladder symptoms and overall quality of life, treatment adherence, and safety and tolerability among patients treated with BCG for NMIBC. NMIBC patients (n=45) will be recruited from the UWMC Uro-oncology Clinic. Baseline data collection will include demographics, clinical characteristics, bladder cancer symptoms, quality of life (QOL), and medication use. Patients are randomized 2:1 to acupuncture (Arm A) and a waitlist control (Arm B). Patients in Arm A receive 6 weekly acupuncture treatments prior to BCG instillation. Patients in Arm B receive coupons for free acupuncture after the completion of treatment. All patients will receive standard symptom management. Follow-up data collection includes baseline measures plus healthcare utilization assessments. The primary objective tests the feasibility, safety and tolabilty of outpatient acupuncture prior to weekly BCG instillations, as assessed by trial recruitment, retention, and adherence to the protocol. Secondary objectives are to compare completion of BCG regimin, urinary symptoms, QOL and use of medications for symptom management between arms. Study results will be used to inform the design of a large-scale trial to test the effect on acupuncture in improving NMIBC treatment adherence.

1.1 Protocol Title

Acupuncture vs. Standard of Care for Induction Intravesical BCG-related Adverse Events in High-Risk Non-Muscle Invasive Bladder Cancer

1.2 Sponsor Information

Early Phase Clinical Research Support Application, Cancer Center Support Grant

1.3 Investigator Information

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1.4 Contractors and Consultants for the Study

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Samia Jannat, Research Coordinator

2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

In 2019, the American Cancer Society estimates that approximately 80,470 Americans will receive new diagnoses of bladder cancer, of which approximately 75% will be new diagnoses of nonmuscle-invasive bladder cancer (NMIBC).(4) As per the American Urological Association (AUA) Guidelines, the cornerstone of management of high-risk, NMIBC is an induction course of 6 weekly instillations of intravesical Bacillus Calmette–Guerin (BCG) treatment following resection of the tumor. (5) Unfortunately, nearly 70% of patients receiving BCG report severe adverse events(6) and approximately 40% of patients receiving induction BCG therapy necessitate treatment interruptions secondary to local or systemic adverse events including pelvic pain, dysuria, severe urgency, frequency, urge incontinence, nocturia, and/or infectious complications.(7) These treatment-associated symptoms are problematic, resulting in decreased ability to adhere to the full course of treatment, which is associated with decreased clinical efficacy of BCG in reducing the risk of recurrence and progression of bladder cancer, as well as severely negatively impacting patients' quality of life. Consequently, there is a need for adjunctive therapies to minimize BCG-associated side effects in order to maximize the likelihood that patients will be able to adhere to the full course of therapy.

Current approaches to managing BCG treatment side effects:
Many of the side effects associated with induction intravesical BCG mirror those of overactive bladder syndrome (OAB). Commonly, the irritiative voiding complaints are managed symptomatically with anticholinergic medications, while bladder pain and dysuria are treated with local analgesics, antibiotics, nonnarcotic pain medications and narcotics, which may or may not be successful in mitigating the severe adverse events associated with intravesical BCG instillatio, and which, furthermore, may be associated with dose-limiting side effects themselves. Indeed, the most commonly prescribed anticholinergic, oxybutynin, was demonstrated to be associated with an increase in lower urinary tract symptoms compared to placebo in a recent randomized controlled trial.(8)

2.2 Preclinical Data

Acupuncture as a potential treatment to increase BCG treatment adherence:
Recently, the use of acupuncture has been shown to be clinically effective in minimizing the severity of OAB symptoms, resulting in decreased medication use and decreased need for surgical treatment of OAB, while simultaneously having an excellent safety and tolerability profile.(9-14) *We hypothesize that acupuncture may be a viable approach to decrease the symptoms akin to OAB secondary to intravesical BCG instillations for high-risk bladder cancer.*

Data from animal studies suggest several physiologic mechanisms of action of the beneficial effects of acupuncture on overactive bladder (OAB) syndrome, including modulating the voiding reflex by decreasing intravesical (bladder) pressure and facilitating storage through inhibiting bladder muscle motor activity.(9) (12) (15) Human trials in OAB show that acupuncture is associated with improvements in urgency, frequency, nocturia, incontinence, quality of life and some objectively measured improvements in urodynamic testing.(9, 10, 16) Additionally, acupuncture has been shown to have comparable effects to anticholinergic drugs in the reduction of micturition episodes in 24 hours, increased void volumes and reduction in OAB symptom score with fewer reported side-effects. (9, 10, 16) Percutaneous Tibial Nerve Stimulation (PTNS), an established FDA-approved second-line treatment option for refractory OAB, is derived from acupuncture theory and techniques.

2.3 Clinical Data to Date

To our knowledge, there are no specific data on the efficacy of acupuncture on improving treatment adherence to induction intravesical BCG. However, as noted above, data on the effect of acupuncture in other related clinical conditions suggest that this is a reasonable application of acupuncture to pursue. Data from animal studies suggest several physiologic mechanisms of action of the beneficial effects of acupuncture on overactive bladder (OAB) syndrome, including modulating the voiding reflex by decreasing intravesical (bladder) pressure and facilitating storage through inhibiting bladder muscle motor activity.(9, 12) (15) Human trials in OAB show that acupuncture is associated with improvements in urgency, frequency, nocturia, incontinence, quality of life and some objectively measured improvements in urodynamic testing.(9, 10, 16) Additionally, acupuncture has been shown to have comparable effects to anticholinergic drugs in the reduction of micturition episodes in 24 hours, increased void volumes and reduction in OAB symptom score with fewer reported side-effects. (9, 10, 16) Percutaneous Tibial Nerve Stimulation (PTNS), an established second-line treatment option for refractory OAB, is derived from acupuncture theory and techniques.

2.4 Study Intervention

Acupuncture is a medical intervention in which fine metallic needles are inserted into anatomical locations of the body to stimulate the peripheral and the central nervous system.

2.5 Dose Rationale

Acupuncture dose. Clinically, the number of acupuncture treatments required depends on the condition being treated and the individual response to acupuncture. The standard course of acupuncture treatment is one to two sessions a week for four to ten weeks.(17) Most acupuncture trials in the US have a dose of one to two treatments per week for six to ten weeks. Given the standard dosing frequency of BCG instillations is once per week for six weeks, which is also a reasonable treatment frequency for acupuncture, the acupuncture dose is once per week for six weeks.

2.6 Risks/Benefits

Acupuncture is generally considered safe(18) when administred by a trained licensed acupuncturists. The risks of acupuncture are few and include minor bruising, bleeding, pain, redness, itchiness, and/or local allergic reactions at the insertion site(s). In rare instances, syncope, infection, or organ puncture can occur.(13)

3.0 OVERVIEW OF CLINICAL TRIAL

The overall objective of this proposal is to evaluate the feasibility and impact of 6 weekly acupuncture treatments compared to a waitlist control on patient-reported bladder symptoms and overall quality of life, treatment adherence, and safety and tolerability among patients being treated with BCG for NMIBC.

3.1 Study Objectives

3.1.1 Primary Objectives

Primary objective: To test the feasibility and safety of integrating an outpatient acupuncture protocal prior to weekly BCG instillations into the Urology Clinic workflow. This will be assessed by trial recruitment, retention, protocol adherence, patient/provider feedback and adverse events.

To achieve this objective, we will:

1. Evaluate the recruitment, rentention and protocal adherence to acupuncture treatment.
2. Survey clinic staff regarding the impact of this intervention on clinical workflow, delays, and clinic burden.
3. Measure physician reported CTCAE v5.0 adverse events specific to acupunture.

3.1.2 Secondary Objectives

To test whether acupuncture may help patients complete the 6-weekly instillations of intravesical BCG. This will be assessed through a patient's completion of BCG regimen, patient-reported outcomes of urinary symptoms and overall quality of life (as measured by the EORTC QLQ-NMIBC-24(1) and EORTC QLQ-C30(2) scales, respectively) and quantification of medication use for symptom management.

To achieve this objective, we will:

1. Compare rates of BCG treatment adherence between arms, as measured by treatment completion, treatment interruptions, and tolerance of treatment retention as measured by time retained, and dose reduction.
2. Compare patient-reported outcomes of urinary symptoms and overall quality of life between arms, as measured by the EORTC QLQ-NMIBC-24 and EORTC QLQ-C30 scales, respectively.

Quantify and compare use of medications for symptom management in patients in the intervention and waitlist control arms, as measured bymedication use questionnaire.

3.2 Study Population

The University of Washington Medical Center (UWMC) Department of Urology Clinic administers BCG to high-risk NMIBC patients receiving either induction or maintenance therapy approximately 40-50 times monthly. We will recruit 45 BCG-adults from the UWMC Department of Urology who are scheduled to receive 6 weekly doses of intravesical BCG. Patients

will be indicated to receive BCG by their primary treating urologist following evaluation of histology from bladder biopsy and/or transurethral resection of bladder tumor tissue, as part of guideline-based standard of care.

Eligibility criteria includes 1) age 18 years or older, 2) English-speaking, 3) diagnosis of American Urological Association (AUA) high-risk NMIBC, including high grade (HG) pT1 (invading only the lamina propria of the bladder), recurrent HG pTa (superficial tumors), HG pTa >3cm in size or multifocal, any carcinoma in situ, any variant histology, any lymphovascular invasion, and HG prostatic urethral involvement(3), 4) have not received acupuncture in the previous 3 months, and 5) willing and able to participate in trial activities. A member of the research team will manually review weekly schedules of full-time uro-oncology faculty (n=6) and fellows (2) to identify patients who meet eligibility criteria as potential study subjects. Patients eligible to participate in the study will be approached by PI/Attending Physician/Advanced Practice Provider/ in the clinic following their post-operative visit during which pathology is discussed and they are counseled regarding BCG induction therapy. Study details will be provided to the patient and informed consent will be discussed at this time. If informed consent is granted, the patient will enter into this trial. Patients who provide consent will be randomized 2:1 to receive weekly acupuncture pre-BCG treatment plus standard of care symptom management (Arm A) or to the waitlist control arm (Arm B), standard of care symptom management plus four coupons for acupuncture after study completion.

3.3 Study Design

Baseline data collection. Prior to initiation of induction BCG, baseline data will be collected at the time of randomization, or at a subsequent baseline study visit or via the phone,email or mailing, depending on patient preference.

Baseline data collection will include 1) clinicopathologic and demographic data; 2) a patient-reported voiding and symptoms assessment using the EORTC QLQ-NMIBC-24 Survey, a validated quality of life questionnaire assessing the domains of urinary symptoms including OAB symptoms, malaise, intravesical treatment issues, future worries, bloating/flatulence, sexual function/intimacy, concerns regarding risk to partners related to therapies designed specifically for patients with NMIBC; 3) patient-reported quality of life as assessed via the EORTC-QLQ-C30 Survey, a validated generic quality of life instrument assessing the domains of depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities ranked on a 4-point Likert scale with an additional 7-point rating scale for overall health and quality of life; 4) current medication use; and 5) current use of complementary, alternative and integrative therapies 6) acupuncture expectancy and treatment preference.

Induction BCG procedures. Patients undergoing induction BCG present once weekly to the UWMC Urology Clinic. They are routinely requested to present 1 hour prior to their scheduled intravesical instillation at which time a urinanalysis is obtained to rule out gross hematuria or concern for urinary tract infection. They are then brought into the clinic exam room where a foley catheter is placed by a nurse or advanced practice provider. The bladder is emptied completely. Then the BCG solution (50mL) is instilled into the catheter over 1-3 min by gravity. The catheter is removed, and the patient discharged from clinic. Patients are instructed to attempt to maintain the medication in their bladder (avoid voiding) for two hours, at which time they may void the medication normally with appropriate precautions to ensure deactivation of the live attenuated vaccines. This procedure is repeated weekly for six weeks. If patients report gross blood in the urine or are found to have a urinalysis consistent with urinary tract infection at the time presentation, or are having severe symptoms of cystitis or bladder pain, treatment is deferred for that week in consultation with their treating physician.

Arm A: Acupuncture intervention. After providing a urinary sample for a screening urinanalysis prior to BCG treatment, patients randomized to the acupuncture intervention will be escorted to a consultation room where they will meet with the study acupuncturist. Over the next 45-60 minutes the following protocol will be implemented:

Position. The patient will lay in a comfortable position on a portable acupuncture table. Specifically, the patient will lay in the lateral recumbent position on their preferred side.

Acupoints. Standard techniques for point location(19) will be utilized and Clean Needle Technique(20) will be followed. See Figure 2 for acupoint locations. The acupuncture points will be needled unilaterally at KI3, KI7, KI10, and SP6 on the lower leg. On the contralateral sided LI11 and LU7 will be needled on the upper extremity. The points BL31, BL32, and BL33 will be needled bilaterally near the sacrum. The points Yin Tang (EX-HN3) and DU20 will be needled on the midline and auricular Shen Men will be needled unilaterally on the same side as the upper limb points. There will be a total of 15 needle sites. Electro-stimulation will be administered to SP6 and KI7 at 1-10mA with a frequency of 20Hz. Needles will be retained for 30 minutes. Specific acupoint selection is based on previously published studies,(9, 10, 16) indications according to Traditional

Chinese Medicine (TCM) theory(19) and current understanding of innervation and neuromodulation of acupoints.(12),(15) After the 30 minute-long treatment, the needles will be removed and the patient will be moved to the treatment room where BCG will be administered according to standard protocol.

Acupuncture needles. 32-40-gauge x 30mm-40mm Seirin acupuncture needles will be used on all acupoints. The needles and guide tubes are individually packaged and sterile. The manufacturer of Seirin acupuncture needles conforms to with GMP, AAMI (American National), ISO 9002, CE Mark (European Common Market), and WHO (World Health Organization) guidelines for quality and safety.(21)

Electroacupuncture. (EA) machines used will be FDA compliant medical devices.(22-24)
Licensing and credentialing of acupuncturists: Acupuncture treatments will be performed by Washington State licensed acupuncturists with National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) certification. Study acupuncturists will be credentialed by the Seattle Cancer Care Alliance (SCCA) and UWMC to provide acupuncture to oncology patients and will be supervised by the Lead SCCA Acupuncturist.

Symptom management. All patients will receive standard of care medications to treat symptoms (e.g. anticholinergics such as oxybutynin, tolterodine, darifenacin, solifenacin, trospium, fesoterodine; Beta-3 adrenergic agonists such as mirabegron, local analgesics such as phenazopyridine, narcotic medications such as oxycodone if necessary, nonnarcotic medications such as Tylenol and non-steroidal anti-inflamatory medications) as indicated.

Arm B: Waitlist control arm. To minimize differences in experience between the acupuncture intervention and waitlist control arms, patients in the waitlist control arm will be escorted to the same Consultation room where the acupuncture is performed and asked to lie in a comfortable position (similar to Arm A) prior to their intravesical therapy for an identical period of time before being moved to a treatment room for intravesical instillation of BCG, according to the standard protocol detailed above. At the conclusion of the trial participants in the waitlist control arm will receive coupons to receive 4 free acupuncture appointments. All patients will receive standard of care to treat symptoms (e.g. narcotic and nonnarcotic medications, local analgesics, anticholinergic medications) as indicated.

Follow-up data collection. On a weekly basis, prior to BCG instillation and adjunctive acupuncture therapy (if applicable), patients in both the intervention and waitlist control arms will be assessed using the following metrics:

Week 1	EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 Medication Journal Assessment of complementary, alternative, and integrative therapies Acupuncture expectancy and treatment preference
Week 2	EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication Journal
Week 3	EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication Journal
Week 4	EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication Journal
Week 5	EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication Journal
Week 6	EORTC-QLQ-NMIBC-244 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication Journal
Week 7	EORTC-QLQ-NMIBC-24

	EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication Journal Follow-up-assessment of complementary, alternative, and integrative therapies Exit questionnaire

Additionally, weekly, *healthcare utilization* will be measured by the number of patient phone calls and eCare messages regarding intravesical-therapy related complaints and unplanned presentations to the emergency room, clinic, and their local providers.

BCG Treatment adherence to each successive BCG therapy will be measured via receipt of complete induction course (yes/no), need for delay of therapy (if yes, by how long), need for decrease in BCG-dose, timing of need for decrease in BCG-dose.

Intravesical therapy dwell time will be measured by time from BCG instillation to time of first void. Patients will be requested to either text or call the research coordinator for the study upon void. If the research coordinator has not heard from the patient within 4-5 hours of their clinical appointment, they will contact the patient by phone call, text, or email to inquire as to what time the patient voided following BCG instillation.

Adverse events will be recorded on a weekly basis using the CTCAE v5. Patients in the acupuncture arm will be surveyed weekly prior to acupuncture treatments regarding side effects and potential adverse events associated with the intervention using a standardized symptom assessment form.

Intervention implementation metrics will be assessed via the following:

Burden to physicians/healthcare providers will be assessed at bimonthly intervals via surveys on the burden of the acupuncture procedure to clinic workflow, delays in providing care, and overall assessments of trial implementation success.

Timing of visits will be assessed via recording of time of presentation, time of initiation of therapy, and time leaving the clinic.

3.3.1 Primary Endpoint

Objective: To demonstrate trial feasibility, impact of integrating outpatient acupuncture (exposure) prior to weekly BCG instillations into the Urology Clinic workflow, and access safety of treatment protocal. To evaluate the safety and tolerability of acupuncture compared to best supportive care practices in patients with high-risk NMIBC undergoing induction intravesical BCG, as measured by physician reported CTCAE v5.0 adverse events.

Analysis plan: The feasibility outcome will be assessed via the following measures:

1. Compare proportion of patients successfully recruited to the trial from those eligible.
2. Compare proportion of recruited patients successfully retained in the experimental (acupuncture) and control arms.
3. Compare adherence to the protocol (completion of acupuncture treatments in the experimental arm).
4. Describe clinic-staff's responses to surveys assessing the healthcare burden of this protocol and compare timing of patient's experience within the clinic, time spent undergoing the acupuncture therapy for the experimental arm.
5. Track adverse events associated with acupuncture therapy in the experimental arm as completed by a provider administered standardized symptom form across weeks of therapy and describe any complications or adverse effects of the therapy.

Expected results and interpretation: We hypothesize that the study is feasible and can be integrated into the clinical workflow of the UWMC Urology clinic with relatively minimal disturbance of the current procedures given that we will be using a consultation

room which is currently not utilized for clinical visits during the day. Additionally, given that patients are requested to be in clinic 1 hour prior to their BCG instillation, we do not anticipate that this study will place further undue time burden upon patients. We do anticipate problems with study recruitement and retainment in this population and that these patients will have a high level of protocal adherence. We hypothesize that the acupuncture procedures in the experimental arm will be well tolerated without clinically meaningful adverse events other than minimal bruising and occasionally soreness at the needling site.(13, 14)

3.3.2 Secondary Endpoints

Objective: To demostrate impact of acupuncture on BCG adherence on direct and indirect measures that include evaluation of BCG protocal experience, patient-reported outcomes of overall quality of life and urinary symptoms, and quantification of medication usage for symptom management.

Analysis plan:

1. Compare Rates of BCG instillation adherence (out of a possible planned six treatments), treatment interruptions, weeks missed, intravesical BCG dwell times (as measured in minutes), and requirement for dose reductions between the acupuncture and control arms.
2. Compare the responses of patients in the experimental and control arms to the EORTC-QLQ-NMIBC-24 symptom index, which was specifically designed to assess bladder and bowel symptoms for patients with NMIBC including assessments of impact of intravesical therapy, and the EORTC-QLQ-C30 , which assesses general quality of life. These assessments will be compared between patients by week of treatment (from week 1 to week 6).
3. Median weekly pill counts standardized by dosage across medication types will be compared between the experimental and control arms by week of therapy. Patients will be given a weekly medication diary and asked to record the number of pills/doses taken per day of specific medications which are administered for bladder symptom management while undergoing intravesical therapies. This pill diary will include topical analgesics such as phenazopyridine, anticholinergic medications, Beta-3 adrenergic receptor agonists (e.g. mirabegron), systemic pain medications including acetaminophen, nonsteroidal anti-inflammatory agents, narcotics, and other naturopathic therapies targeted at symptoms of dysuria, bladders spasms, and pelvic pain.

Expected results and interpretation: We hypothesize that patients in the experimental group will have higher proportion finishing BCG regimen, with less interuptions and fwere required dose reductions of BCG. We hypothesize that patients in the experimental group will report similar general quality of life and NMIBC-specific symptoms initially. However, as patients advance in their treatments from 1 to 6 weeks, we anticipate that patients in the experimental arm will endorse improved quality of life and lower levels of bladder/bowel symptoms compared to the control arm. Furthermore, we predict that patients randomized to the experimental arm will have higher rates of protocol retention, treatment adherence, and median intravesical dwell times of the BCG at each treatment. We hypothesize that patients in the experimental arm will report taking lower amounts of adjunctive medications for bladder-relates symptoms and that the discrepancy in adjunctive treatments taken will increase across the 6 weeks of therapy as the BCG-related symptoms are expected to increase with each subsequent intravesical dose of BCG.

3.4 Estimated Accrual

The University of Washington Medical Center (UWMC) Department of Urology Clinic administers BCG to high-risk NMIBC patients receiving either induction or maintenance therapy approximately 40-50 times monthly. We will recruit 45 BCG-adults from the UWMC Department of Urology who are scheduled to receive 6 weekly doses of intravesical BCG.

3.5 Name of Sponsor/Funding Source

Sponsor: Early Phase Clinical Research Support Application, Cancer Center Support Grant
Award ID# P30 CA015704-44

4.0 SAFETY CONSIDERATIONS

4.1 Stopping Rules

This trial does not contain stopping rules.
Patients will be monitored for BCG-related toxicity as per standard of care practice. Modifications to BCG dosing and intervals between treatment will be made on a per-patient basis per usual care.

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion Criteria

5.1.1 Demographic Data

1) 18 years of age or older
2) English-speaking

5.1.2 Disease Related Criteria

3) Diagnosis of American Urological Association (AUA) high-risk NMIBC, including high grade (HG) pT1 (invading only the lamina propria of the bladder), recurrent HG pTa (superficial tumors), HG pTa >3cm in size or multifocal, any carcinoma in situ, any variant histology, any lymphovascular invasion, and HG prostatic urethral involvement(3)
4) Diagnosis with urothelial carcinoma (primary histologic subtype), localized ot the bladder, in the absence of nodal or other visceral metastases.
5) Patients who have been indicated for induction intravesical BCG in shared-decision-making with their primary urologist.

5.1.3 Prior/Current Related Criteria

6) Have not received acupuncture in the previous 3 months.

5.1.4 Accessibility Criteria

7) Access to phone for study contacts.
8) Willing and able to participate in trial activities

5.1.5 Clinical/Laboratory Criteria

9) Platelets: 20,000/ μL or greater
10) ANC: 500 cells/μL or greater

5.1.6 Ability to understand and the willingness to sign a written informed consent document.

11) Able to understand and willing to sign written informed consent in English.

5.2 Exclusion Criteria

5.2.1 Receipt of prior therapy

Subjects who have had intravesical or systemic chemotherapy or radiation therapy for bladder cancer or for other malignancies prior to entering the study.

5.2.2 Subjects may not be receiving other investigational agents or other combined intravesical therapies.

Subjects who are indicated to receive other intravesical agents or therapies concurrently with BCG will be excluded.

5.2.3 Disease-specific criteria

Subjects who have muscle-invasive bladder cancer, radiographic evidence of lymph node metastases or metastatic disease involving other organs including brain metastases.
Patients with predominant histology other than urothelial carcinoma of the bladder who would not otherwise be considered candidates for BCG.

5.2.4 Contraindications to receiving intravesical BCG

BCG is contraindicated in:

- Patients who are pregnant or lactating
- Patients with active tuberculosis
- Immunosuppressed patients with congenital or acquired immune deficiency, whether due to concurrent disease (e.g. AIDS, Lymphoma, Leukemia), concomitant cancer therapy (cytotoxic drugs, radiation), or immunosuppressive therapy (e.g. corticosteroids, DMARDs).
- Symptomatic urinary tract infection
- Febrile illness
- Patients requiring chronic treatment with certain antibiotics that may interfere with the effectiveness of BCG.
- Any previous allergies or severe reactions to BCG

5.2.5 Contraindications to Accupuncture/Electrostimulation

- Not pregnant or trying to become pregnant. Acupunture points included in the protocol are contraindicated with pregnancy.
- Does not have a pacemaker. There is potential of electrostimulaton interfering with the operation and function of pacemakers.

5.2.6 Address concomitant medications which may have an effect on the pharmacokinetics of the investigational agent.

- Patients requiring chronic treatment with certain antibiotics that may interfere with the effectiveness of BCG. Fluoroquinolone therapy may decrease the efficacy of intravesical BCG. Antibiotic therapy for ongoing treatment of active tuberculosis will decrease the efficacy of intravesical BCG.

5.2.7 Uncontrolled or concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

5.2.8 Address excluding pregnant women from the study.

1) Pregnant women are excluded. Acupunture points included in the protocol are contraindicated with pregnancy and BCG is contraindicated in pregnancy.

5.2.9 Any additional exclusion criteria and the rationale.

2) Pacemaker. Patients with pacemakers are restricted due to the potential of electrostimulaton interfering with a pacemakers operation.
3) Platelets: < 20,000/ μL. Risk of bleeding with acupuncture
4) ANC: < 500 cells/μL. Risk of infection with acupuncture
5) Received acupuncture in the previous 3 months. Acupuncture treatment effects persist after a course of treatment, previous exposure to the intervention has the potential to affect the baseline data for treatment and control arms.(25)

6.0 SUBJECT REGISTRATION

Subjects will be registered by the Fred Hutch/UW Study Coordinator and entered into the OnCore CTMS. A complete, signed, study consent and HIPAA consent are required for registration.

7.0 TREATMENT PLAN

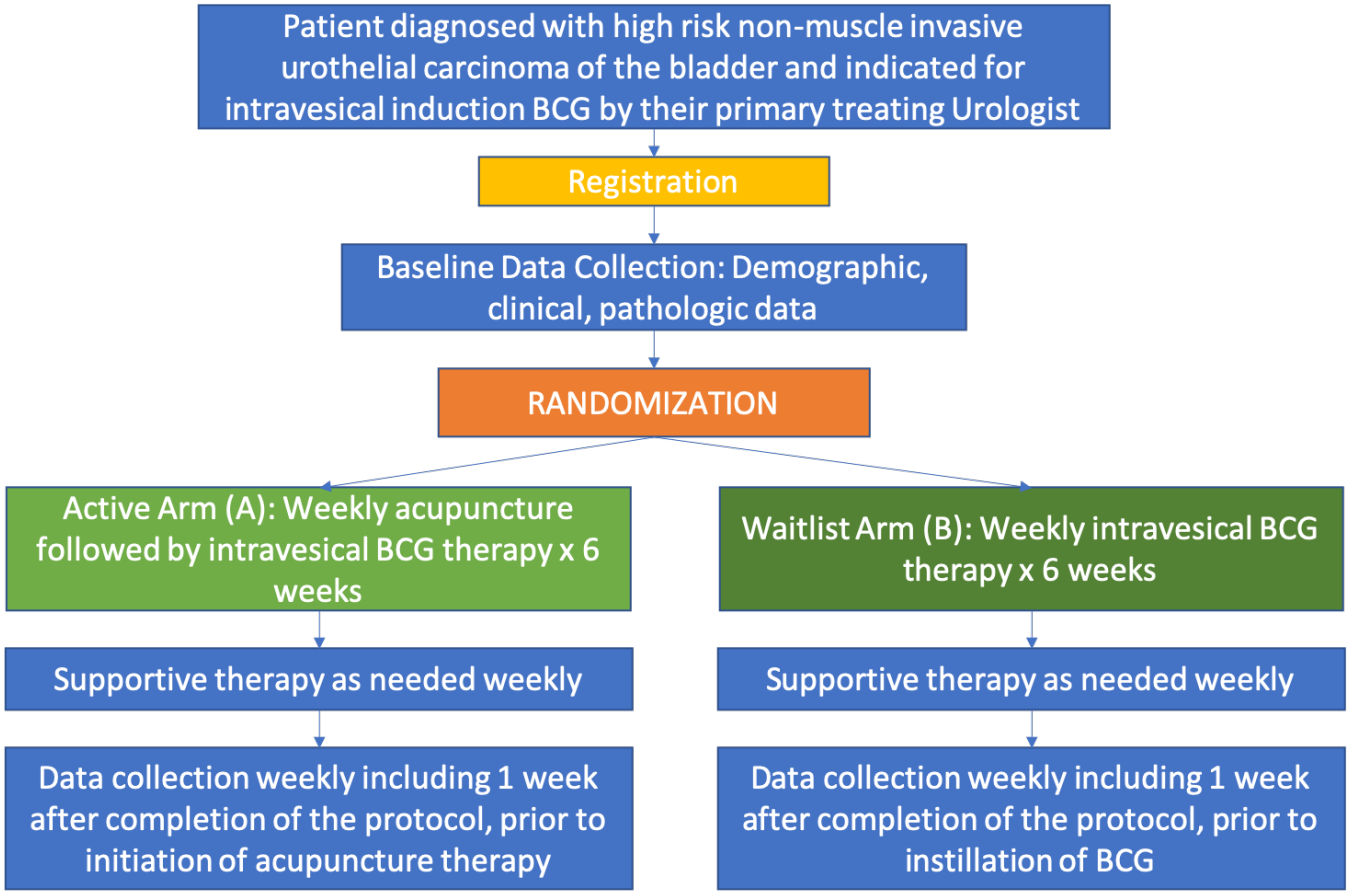
Briefly outline the major treatment components of this protocol including treatment agents, timing and method of administration, setting of administration (inpatient or outpatient), duration of therapy and anticipated toxicities and the method of treatment of these toxicities. Also address the administration of prophylactic or supportive care drugs or regimens and any interactions with the study agent that prohibit the administration of specific concomitant medications.

For those evaluations or procedures that are somewhat flexible in reference to timing, allow for flexibility by stating in the protocol that they may be done “plus or minus” x days. This will further ensure compliance with the protocol.

Outline Treatment Schedule	
Day	***Treatment***
1 +/- 7	*Acupuncture Treatment #1* *BCG Instillation #1*
8 +/- 7	*Acupuncture Treatment #2* *BCG Instillation #3*
15 +/- 7	*Acupuncture Treatment #3* *BCG Instillation #3*
22 +/- 7	*Acupuncture Treatment #4* *BCG Instillation #4*
29 +/- 7	*Acupuncture Treatment #5* *BCG Instillation #5*
36 +/- 7	*Acupuncture Treatment #6* *BCG Instillation #6*

7.1 Treatment Plan Overview

SCHEMA



7.2 Waitlist Control

At the end of the study, participants randomized to the waitlist control group will receive 4 coupons to receive free acupuncture in the Prevention Center at the Fred Hutchinson Cancer Research Center.

7.3 Concomitant Medication, Interruption of Therapy, and Supportive Care Guidelines

- A urine analysis will be performed prior to instillation. If bactiuria is present on high power field or >5 WBCs are present on high power field and/or gross hematuria is noted and/or the patient complains of acute cystitis symptoms (urinary urgency, frequency, dysuria), instillation is deferred and urine is sent for culture to confirm the presence of UTI and sensitivity to culture. Appropriate antibiotic therapy is prescribed per standard of care clinical practice. Findings are discussed with the prescribing clinician. Microscopic hematuria only or isolated WBCs in an otherwise asymptomatic patient do not preclude treatment.
- For patients complaining of bladder spasms, urinary urgency, or frequency: anticholinergic medications such as oxybutynin, tolterodine, darifenacin, solifenacin, trospium, fesoterodine or Beta-3 adrenergic agonists such as mirabegron will be prescribed. For severe refractory bladder spasms, other medications such as benzodiazepines, may be used to relax the bladder.
- For male patients complaining of obstructive urinary symptoms: alpha-antagonists such as tamsulosin may be used.
- For patients complaining of bladder pain, local analgesics such as phenazopyridine may be used. Additionally, narcotic medications such as oxycodone if necessary, nonnarcotic medications such as Tylenol and non-steroidal anti-inflamatory medications) as indicated.
- Patients with fevers, chills, nausea, vomiting, or other systemic symptoms will be directed to their local emergency room, urgent care, urologist's office, or primary care physician as appropriate for further evaluation and management.

7.4 Duration of Therapy

Therapy is administered weekly for a total of 6 weeks. If a patient's therapy is deferred for one week due to infection, gross hematuria, symptoms, or other reasons (e.g. travel, personal reasons why a patient may not attend a scheduled clinic visit, travel issues), patients will resume therapy the next week they are able to do so.

7.5 Duration of Follow-Up

For the purposes of this study, symptom and adverse event evaluation as well as patient-reported outcomes will be collected weekly, including 1 week following completion of BCG therapy. From a bladder cancer standpoint, patients are followed on an ongoing basis, and will generally undergo a subsequent cystoscopy in clinic or the OR for the purpose bladder cancer surveillance within 2-6 weeks of completion of induction BCG to assess efficacy of the treatment and for bladder cancer response vs. persistence and/or progression. No imaging is indicated as per this protocol. However, patients with high risk NMIBC undergo annual CT scans for routine standard of care cancer staging.

7.6 Dosing Delays/Dose Modifications

- A urine analysis will be performed prior to instillation. If bactiuria is present on high power field or >5 WBCs are present on high power field and/or gross hematuria is noted and/or the patient complains of acute cystitis symptoms (urinary urgency, frequency, dysuria), instillation is deferred and urine is sent for culture to confirm the presence of UTI and sensitivity to culture. Appropriate antibiotic therapy is prescribed per standard of care clinical practice. Findings are discussed with the prescribing clinician. Microscopic hematuria only or isolated WBCs in an otherwise asymptomatic patient do not preclude treatment.
- For patients reporting severe bladder pain, bladder spasms, urgency/frequency, in consultation with their primary urologist, the dose of BCG may be decreased to half-strength (25mg/50mL) as indicated.

7.7 End of Treatment (EOT) Visit Schedule and Procedures

EOT Visits for all subjects who discontinue from the study will occur at least 7 days, but ≤ 30 days, after the last dose of intravesical therapy and prior to beginning other treatment. Procedures to be performed during the EOT Visit include:

- Physical Exam
- Vital Signs
- Performance Status
- Labs: urine analysis with reflex culture
- AE Assessment
- Patient Surveys: EORTC-QLQ-NMIBC-24, EORTC QLQ-C30
- Medication List
- List of complementary and alternative therapies

8.0 SUBJECT EVALUATION

8.1 On-Study Clinical Evaluations

Week	*Visit Purpose*	*Procedures/Evaluations*
0	*Enrollment*	*Registration, Collection of Baseline Demographic and Clinical Data, Performance Status, Details regarding the patient's pathology.*
--	*Randomization*	*Patient will be randomized to either Arm A (Acupuncture) or Arm B (Waitlist Control)*
1 +/-7	*BCG Treatment 1*	*Patient will receive BCG instillation #1 with/without acupuncture intervention prior as per their study arm assignment* *Review of Medication List* *Urinanalysis* *Vital signs to include BP, pulse, temperature*

		Assessment of ability to retain intravesical instillation for the desired dwell time (1-2 hours). Anticholinergic medications may be prescribed per clinic protocol if the patient complains of bladder spasms *Brief physical exam: perineal and abdominal inspection and pain assessment (bladder, back, pelvis) before, during, and after instillation)* *Completely drain the bladder prior to instillation of medication for maximum medication concentration in the bladder.* *Assessments as per the schedule in Section 3.3* EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 Medication journal Assessment of complementary, alternative, and integrative therapies for the prior 3 months Acupuncture Expectency and Treatment Preference Questionnaire
2 +/-7	*BCG Treatment 2*	*Patient will receive BCG instillation #2 with/without acupuncture intervention as per their study arm assignment* *Review of Medication List* *Urinanalysis* *Vital signs to include BP, pulse, temperature* *Assessment of ability to retain intravesical instillation for the desired dwell time (1-2 hours). Anticholinergic medications may be prescribed per clinic protocol if the patient complains of bladder spasms* *Brief physical exam: perineal and abdominal inspection and pain assessment (bladder, back, pelvis) before, during, and after instillation)* *Completely drain the bladder prior to instillation of medication for maximum medication concentration in the bladder.* *Assessments as per the schedule in Section 3.3* EORTC- QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication journal
3 +/- 7	*BCG Treatment 3*	*Patient will receive BCG instillation #3 with/without acupuncture intervention as per their study arm assignment* *Review of Medication List* *Urinanalysis* *Vital signs to include BP, pulse, temperature* *Assessment of ability to retain intravesical instillation for the desired dwell time (1-2 hours). Anticholinergic medications may be prescribed per clinic protocol if the patient complains of bladder spasms* *Brief physical exam: perineal and abdominal inspection and pain assessment (bladder, back, pelvis) before, during, and after instillation)* *Completely drain the bladder prior to instillation of medication for maximum medication concentration in the bladder.* *Assessments as per the schedule in Section 3.3* EORTC-QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication journal
4 +/- 7	*BCG Treatment 4*	*Patient will receive BCG instillation #4 with/without acupuncture intervention as per their study arm assignment*

		Review of Medication List *Urinanalysis* *Vital signs to include BP, pulse, temperature* *Assessment of ability to retain intravesical instillation for the desired dwell time (1-2 hours). Anticholinergic medications may be prescribed per clinic protocol if the patient complains of bladder spasms* *Brief physical exam: perineal and abdominal inspection and pain assessment (bladder, back, pelvis) before, during, and after instillation)* *Completely drain the bladder prior to instillation of medication for maximum medication concentration in the bladder.* *Assessments as per the schedule in Section 3.3* EORTC- QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication journal
5 +/- 7	*BCG Treatment 5*	*Patient will receive BCG instillation #5 with/without acupuncture intervention as per their study arm assignment* *Review of Medication List* *Urinanalysis* *Vital signs to include BP, pulse, temperature* *Assessment of ability to retain intravesical instillation for the desired dwell time (1-2 hours). Anticholinergic medications may be prescribed per clinic protocol if the patient complains of bladder spasms* *Brief physical exam: perineal and abdominal inspection and pain assessment (bladder, back, pelvis) before, during, and after instillation)* *Completely drain the bladder prior to instillation of medication for maximum medication concentration in the bladder.* *Assessments as per the schedule in Section 3.3* EORTC- QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication journal
6 +/- 7	*BCG Treatment 6*	*Patient will receive BCG instillation #6 with/without acupuncture intervention as per their study arm assignment* *Review of Medication List* *Urinanalysis* *Vital signs to include BP, pulse, temperature* *Assessment of ability to retain intravesical instillation for the desired dwell time (1-2 hours). Anticholinergic medications may be prescribed per clinic protocol if the patient complains of bladder spasms* *Brief physical exam: perineal and abdominal inspection and pain assessment (bladder, back, pelvis) before, during, and after instillation)* *Completely drain the bladder prior to instillation of medication for maximum medication concentration in the bladder.* *Assessments as per the schedule in Section 3.3* EORTC- QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication journal
7 +/- 14	*Follow-up*	*Review of Medication List*

		Vital signs to include BP, pulse, temperature Physical exam Performance Status EORTC- QLQ-NMIBC-24 EORTC-QLQ-C30 CTCAE v.50 assessment of Systemic Therapy Toxicity assessing symptoms over the prior week Medication journal Follow-up assessment of complementary, alternative, and integrative therapies Exit Questionnaire

9.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study treatment (acupuncture).

If a subject withdraws consent to participate in the study or aspects of the study, we will request permission to record survival data up to the protocol-described end of the subject follow-up period.. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

If a subject withdraws from the study, they will not be replaced. Patients who with-draw or whom are removed from the study by their primary urologist (e.g. in whom their primary urologist determines it is not safe or indicated to proceed with BCG induction due to side effects, other comorbidities, lack of tolerance, or other patient-related concerns) will be surveyed to determine the reason for withdrawal. I.e. An explanation for discontinuing treatment is recorded for each subject discontinuing treatment on the appropriate CRF/eCRF. All subjects, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the Sponsor decides to stop the study;
- at Investigator's discretion;
- at the subject's request;
- if the subject enrolls in a trial of another investigational agent;
- Grade 4 or life-threatening toxicity (See Section 11, Adverse Events) attributable to acupuncture;
- toxicity reactions of Grade 3 or higher, according to the grading in Appendix X - NAME Grading Scale
- pregnancy;
- development of severe BCG toxicity or side effects, e.g. BCG-sepsis, severe refractory BCG cystitis, that preclude the patient from being able to tolerate further BCG instillation.

10.0 CONCOMITANT MEDICATIONS

Patients will have their medication list reviewed and documented in CRF at study entry. On a weekly basis, medication lists will be reevaluated for modifications/changes in presecription. Patients will also be requested to fill out a medication diary regarding the medications taken over the prior week for management of bladder symptoms including urinary urgency, frequency, dysuria, bladder pain, or systemic symptoms such as myalgias, fevers, chills, nausea, vomiting.

Patients may continue to take all of their routine medications:

- Subjects may take doses of nonprescription strength NSAIDS, acetaminophen (paracetamol), ibuprofen or acetylsalicylic acid (aspirin) for non-chronic headache, muscle pain, trauma or prophylaxis as long the dosing regimens comply with the recommended dose in the product labeling.
- Subjects may receive antihistamine therapy for colds or allergies at non-prescription doses.
- Subjects may take vitamin supplements within a dose range not associated with toxicity.
- Other treatments and medications that may affect immune function, that have known or suspected anti-tumor activity, or that could interfere with the imaging assessment of disease progression are not allowed for subjects including any and all chemotherapeutics.

- The use of other investigational agents is not permitted.
- Active immunotherapy is not allowed for any subject.
- Any antibiotic therapy or antimicrobial therapy will be disclosed at the start of each visit. Patients may take antimicrobial therapy as indicated for active infection.

11.0 ADVERSE EVENTS

11.1 Adverse Event

According to ICH guidelines (Federal Register. 1997; 62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.

Medical conditions present at screening (i.e., before the study treatment is administered) are not adverse events and should not be recorded on adverse event pages of the CRFs. These medical conditions should be adequately documented on the subject chart. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as adverse events.

11.2 Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

11.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and

reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

11.4 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

11.5 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

11.6 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- Definite: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- Probable: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Possible: The event follows a reasonable temporal sequence from exposure to the investigational agent, but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unlikely: Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

11.7 Adverse Event Recording Period

AEs will be monitored and recorded in study-specific case report forms (CRFs) from the time of first exposure to acupuncture.

11.8 Adverse Event Reporting Requirements

11.8.1 Reporting to IRB

The investigator will report events to the FHCRC IRB in accordance with the policies of the IRB.

12.0 DATA AND SAFETY MONITORING PLAN

There will be no external monitoring conducted for this study, given the low risk nature of this trial, minimal risk to participants and single institution nature of the study. The trial will be reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee.

13.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

Subject research files are stored in a secure place, locked in the Research Coordinator's office for Urologic Oncology within the Urology Clinic at UWMC. Electronic records will be maintained in a HIPAA compliant, password-protected RedCAP database maintained by the study PI and research coordinator. Access is restricted to authorized personnel. Records will not be shared with any external personnel.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a pilot randomized control trial. Patients who provide consent will be randomized 2:1 to receive weekly acupuncture pre-BCG treatment plus standard of care symptom management (Arm A) or to the waitlist control arm (Arm B), standard of care symptom management plus four coupons for acupuncture after study completion.

14.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

14.2.1 Primary Endpoint

1. Trial recruitment (proportion enrolled versus eligible, reason for not enrolling) will be described via qualitative report.
2. Trial retention (proportion retained versus all enrolled, reason for not completing) will be described via qualitative report. Successful retention is defined as continued participation within the trial until 1 week following completion of induction BCG.
3. Protocol adherence (proportion adhered versus all enrolled, specifics for how protocal was not followed and why) will be described via qualitative report. Protocol adherence is defined as completion of the acupuncture interventions and follow-up surveys if randomized to the acupuncture arm or completion of the follow-up surveys if randomized to the control arm.
4. Clinic staff's responses to surveys assessing the healthcare burden of this protocol and time spent undergoing the acupuncture therapy for the experimental arm will be described via qualitative report.
5. Adverse events associated with acupuncture therapy in the experimental arm will be described via qualitative report.

14.2.2 Secondary Endpoints

1. BCG instillation adherence out of a possible planned six treatments (**successful adherance** defined as the number of successfully administered BCG instillations (of a possible 6 total)), **treatment interruptions** (defined as number of weeks that a BCG instillation was delayed) , **weeks missed** (measured as any vs none, and total weeks that BCG was not administered of the planned 6 weekly induction doses of intravesical BCG), **intravesical BCG dwell times** (measured

in minutes), and **requirement for dose reductions** (measured as yes/no) between the acupuncture and control arms will be compared via t-test and chi-square as appropriate.

2. Responses of patients in the experimental and control arms to the EORTC QLQ-NMIBC-24(1) and EORTC QLQ-C30(2) symptom index will be compared via t-test at each time point.
3. **Median weekly pill counts** of medications prescribed for the management of BCG-related side effects, standardized by dosage across medication types, will be compared via Wilcoxen rank sum test.

14.3 Sample Size and Power

This study will have a sample size of 45 with 2:1 for treatment to control arm. The primary outcome is feasibility. This outcome is assessed through a mix of qualitative reports (trial recruitment, retention, protocol adherence, patient/provider feedback and evaluation of adverse events). For the qualitative reports there is no statistical testing, thus there is no formal power analysis. Based on prior experience we felt we needed at least 15 patients in each arm are to assess these factors quantitatively. For the patient survey, the two arms will be compared using t-test. For a trial designed with 90% power and two-sided 5% significance, we did the recommended pilot trial sample sizes per treatment arm of 15 for small standardized effect sizes (0.2) with continuous data(26). This sample size should also apply to continuous secondary endpoints. Extrapolating this reference point, we then doubled the treatment arm size in order assess some of the secondary endpoints within the treatment arm (e.g. responses of patients to the EORTC- QLQ-NMIBC-24 symptom index). Lastly, for a two-sample proportions test at 80% power and 5% significance, we calculated being able to observe a 0.4 difference between the 2 groups for binomial endpoints.

14.4 Analysis of Covariates

As this is a pilot study we do not have adequate power to adjust for covaraites such as age, gender, and existing comorbidities.

14.5 Ethnic and Gender Distribution Chart

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects = 45			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	1	2	3
Not Hispanic or Latino	9	33	42
Ethnic Category Total of All Subjects*	10	35	45
Racial Categories			
American Indian / Alaska Native	1	3	4
Asian	1	3	4
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	1	1	2
White	6	27	33
More Than One Race	0	0	0
Racial Categories: Total of All Subjects*	10	35	45

14.6 Indications for Stopping

Patients participation will be terminated for the following indications:

- If they express a preference to no longer part in the study/personal preference.
- For major side effects or toxicities or complications associated with acupuncture resulting in patient request to not continue
- If the study investigators determine that it is no longer safe or feasible for a patient to continue to receive BCG or acupuncture due to progression of bladder cancer or other comorbid conditions.

15.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after studycompletion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures (see Appendices 1).

16.0 REFERENCES

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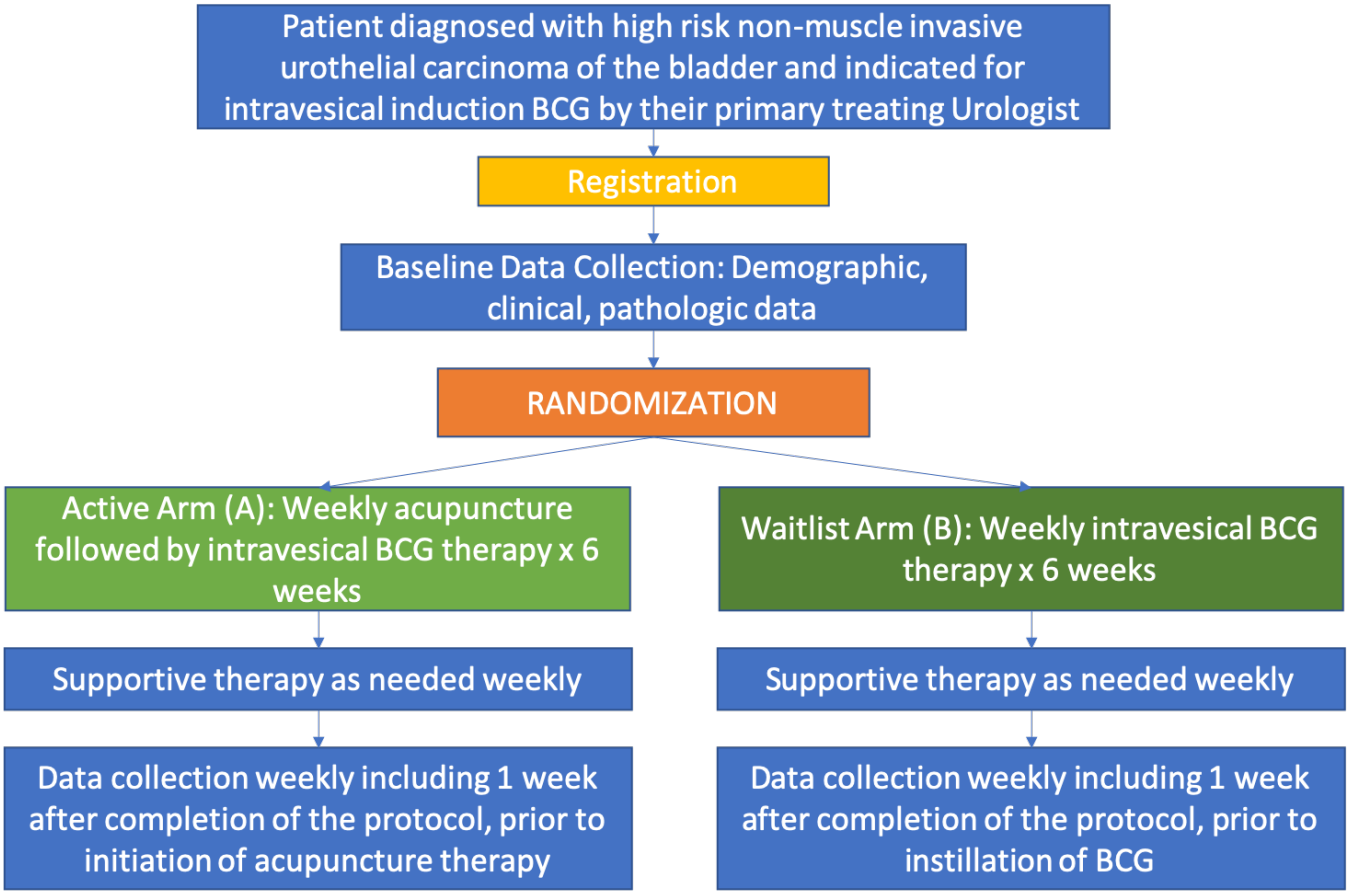
17.0 APPENDICES

Appendix A: Sample Schema
Appendix B: ECOG Performance Status Scale
Appendix C: Acupoint Location Diagram
Appendix D: Study Calendar

APPENDIX A – Study Schema

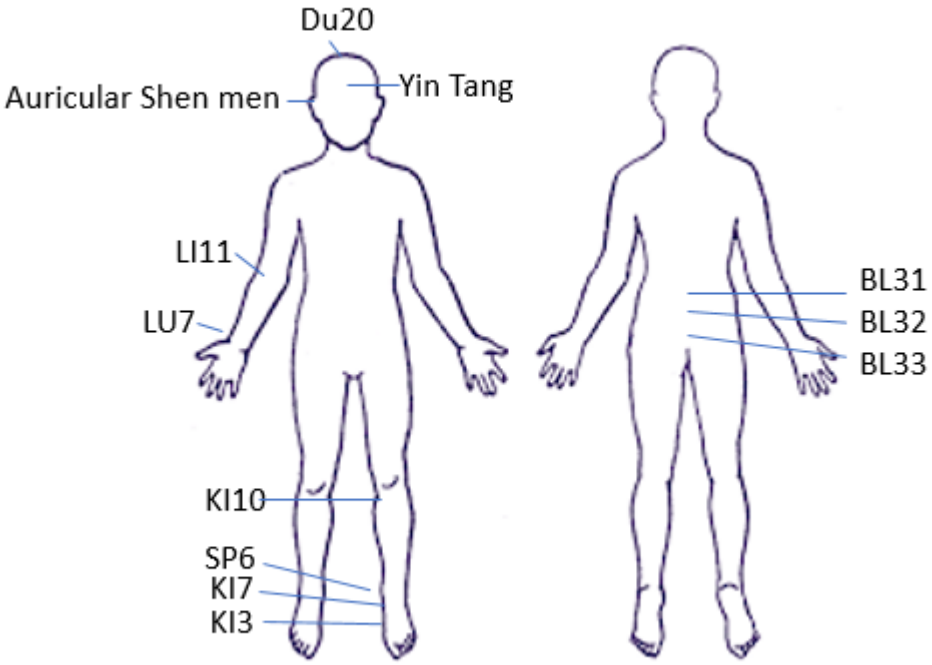


APPENDIX B – ECOG Performance Status Scale

ECOG Performance Status Scale

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX C: Acupoint Location Diagram



APPENDIX D: STUDY CALENDAR

Study Calendar

	Screening	**Baseline data**	**Week 1 BCG 1**	**Week 2 BCG 2**	**Week 3 BCG 3**	**Week 4 BCG 4**	**Week 5 BCG 5**	**Week 6 BCG 6**	**Week 7 Follow Up**
Procedure	within X days	1 week prior to BCG #1 +/- X Days	Day 1	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days
Physical Exam	X		X	X	X	X	X	X	X
Medical History Clinicopathologic		X							
Demographic Data		X							
Current Use of CAM/IM		X							
Informed Consent		X							
ECOG	X								X
EORTC-QLQ-NMIBC-24			X	X	X	X	X	X	X
EORTC-QLQ-C30			X	X	X	X	X	X	X
CTCAE v5				X	X	X	X	X	X
Assessment of CAM/IM Use		X	X	X	X	X	X	X	X
Medication Journal			X	X	X	X	X	X	X
AE to Study Intervention				X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X
UA			X	X	X	X	X	X	
Study Intervention Therapy			X	X	X	X	X	X	
Foley Cath bladder emptied			X	X	X	X	X	X	
BCG			X	X	X	X	X	X	
Bladder Void Time recorded			X	X	X	X	X	X	