Evidence-based Practice Center Systematic Review Protocol

Project Title: Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer

I. Background and Objectives for the Systematic Review

Nature and burden of non-muscle-invasive bladder cancer

Bladder cancer is the fourth most commonly diagnosed cancer in men and tenth most commonly diagnosed cancer in women in the U.S.[1] The American Cancer Society estimates there will be 72,570 new cases of bladder cancer in the U.S. in 2013 (about 54,610 men and 17,960 women), and about 15,210 deaths due to bladder cancer (about 10,820 men and 4,390 women).[1] The lifetime probability of developing bladder cancer in the U.S. is approximately 3.8 percent in men and 1.2 percent in women, although the incidence of bladder cancer is increasing in women. Bladder cancer occurs primarily in men older than 60 and roughly twice as frequently in white compared to black men,[2] though mortality is similar, presumably due to delayed diagnosis in black men.

Bladder cancer remains an important health problem, with no improvement in associated mortality since 1975.[3] Economic analyses have shown bladder cancer to be the costliest cancer to treat in the U.S. on a per capita basis, taking into account diagnostic testing, management, and long term follow up.[4] The most common risk factor for bladder cancer is smoking, though other risk factors include occupational exposures and family history. The most common symptom of bladder cancer is painless hematuria (blood in the urine).

Bladder cancer is staged based on the extent of penetration or invasion into the bladder wall and adjacent structures.[5] Bladder cancers that have not invaded the bladder smooth muscle layer (stage classifications Tis carcinoma in situ, Ta noninvasive papillary carcinoma, and T1 cancer that invades the subepithelial connective tissue) are broadly grouped as non-muscle-invasive bladder cancers (Non-MIBC). Stage 2 cancers are muscle-invasive, and higher stage cancers invade beyond the muscle layer into surrounding fat (stage classification T3 bladder cancer) or beyond the fat into nearby organs or structures (stage classification T4 bladder cancer). Approximately 75 percent of newly diagnosed bladder cancers are Non-MIBC.[6] Individuals with Non-MIBC have a good prognosis. In general, these cancers are not life threatening and have five-year survival rates higher than 88 percent.[7] As many as 70 percent of Non-MIBC tumors will recur after initial treatment, with a 10-20 percent risk of progression to invasive bladder cancer.[6] The likelihood of progression to more invasive cancer is associated with the presence of more poorly differentiated cells and other histopathological features. Prognosis is poorer for patients with more invasive Stage 2 or higher bladder cancers (5-year survival rates from 63 to 15 percent).[7]

Diagnosis and surveillance of bladder cancer

A number of tests are available for screening, diagnosis and staging of bladder cancer. Urine dipstick and microscopic urinalysis in order to detect hematuria, and urine cytology in order to detect abnormal or cancerous cells in the urine, followed by imaging

tests and cystoscopy have historically been used to identify bladder cancer and are considered the reference standard.[8] More recently, urine-based biomarkers have been developed as potential diagnostic alternatives to imaging, cytology and cystoscopy.[9] Biomarkers including bladder tumor-associated antigen (BTA); nuclear matrix protein 22 (NMP22); various chromosome abnormalities (detected using techniques such as fluorescence in situ hybridization [FISH] assay or mRNA); fibroblast growth factor receptor 3 (FGFR3); cytokeratin fragments (e.g., CYFRA 21-1, TPA, TPS); survivin; telomerase; vascular endothelial growth factor (VEGF); aurora kinase, metalloproteinases (MMP-2 and MMP-9); carcinoembryonic antigen (CEA); and mucin glycoproteins have been evaluated in conjunction with cytology, with the hope that they may eventually replace the more invasive cystoscopy for diagnosis. In addition to diagnosis and staging, diagnostic surveillance is required following treatment, to identify patients with recurrence or progression of cancer. Many of the new urine-based biomarker tests are also used for surveillance for recurrence or progression, with the same goal of eventually replacing cystoscopy. Many of the tests are investigational. There are five diagnostic biomarker tests approved by the FDA for diagnosis or surveillance of bladder cancer: BTAstat® (BTA), Alere NMP22®, BladderChek® (NMP22), UroVysion® (FISH) and ImmunoCyt™ (uses monoclonal antibodies to test for CEA and mucin glycoproteins using an immunofluorescent technique). The CxBladder™ test, which tests for five specific mRNA biomarkers, is a "Laboratory Developed Test" that does not require FDA approval. The large number of available tests and testing strategies and potential trade-offs in diagnostic accuracy, risks, and patient preferences pose significant challenges in determining optimal testing and monitoring strategies. Tests with high false positive rates could lead to unnecessary invasive procedures for further evaluation and tests with high false negative rates could lead to missed diagnoses.

Interventions and outcomes for non-muscle-invasive bladder cancer

Once bladder cancer has been diagnosed, a number of factors affect prognosis and treatment options. These include the stage of the cancer, tumor grade, whether the tumor is an initial tumor or a recurrence, the patient's age and general health, and other factors. The main treatment for Non-MIBC is local resection with transurethral resection of the bladder tumor (TURBT), often with adjuvant intravesical therapy, such as the immediate post-TURBT instillation of chemotherapy (e.g., mitomycin, apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin) or the use of adjuvant intravesical Bacillus Calmette-Guerin (BCG) or interferon immunotherapy.[10] All of these treatments are FDA approved and available in the US. Electromotive drug administration (EMDA) is a method for enhancing the effectiveness of intravesical chemotherapy that is increasingly used, especially in Europe. Clinical trials of EMDA are ongoing in the US, but the method is not widely available or FDA approved.

Some patients may not receive adjuvant therapy immediately post-TURBT due to potential side effects, potentially increasing the risk of recurrence or progression. The European Association of Urology advocates an assessed risk-adapted approach to treatment decision-making, based on available prognostic factors including grade, stage, number and size of tumors.[11] This approach, which stratifies patients into three risk groups, may be especially useful for patients in the intermediate and high risk groups.

Rationale for evidence review

     The comparative effectiveness of the diagnostic tests and treatments for Non-MIBC is uncertain. Existing guidelines for the treatment and follow up of Non- MIBC from the European Association of Urology were published in 2011.[11] Since publication of that review there have been numerous randomized controlled trials, controlled clinical trials, comparative studies and cohort studies. Much of this literature focuses on diagnostic techniques such as fluorescence cystoscopy or urine-based biomarkers, and treatments with intravesical therapy including mitomycin and BCG. A systematic evidence review that includes recently published research may provide a better understanding of the comparative effectiveness of these approaches to diagnosis, treatment, and post-treatment surveillance for Non-MIBC. The systematic review may be used to update existing clinical recommendations that are several years old and may be out-of-date due to the development of new technologies and therapies.

II. The Key Questions

     The Agency for Healthcare Research and Quality (AHRQ) initially received this topic as a nomination via the Effective Healthcare Website (http://www.effectivehealthcare.ahrq.gov/submit-a-suggestion-for-research/read-suggested-topics-for-research/?pageAction=view&topicID=587&source=current). The Scientific Resource Center (SRC) developed preliminary Key Questions (KQs) based on input from the topic nominator. The Evidence-based Practice Center (EPC) revised the KQs and developed eligibility criteria to identify the populations, interventions, comparators, outcomes, timing, and study designs (PICOTS) of interest. The EPC further refined the KQs and PICOTS based on input from interviews with the Key Informants. The KQs and PICOTS were then posted for public comment from February 6, 2014 through February 26, 2014, and comments were received from two individuals. In response to public comments, the EPC revised the wording of KQ 2 to specify "use of a formal risk-adapted assessment approach", and added "cystectomy" as a comparator of interest to KQ 3 and KQ4. Based on additional input from a Technical Expert Panel (see section X below), the EPC removed a question on electromotive therapy (not available in the United States), added surveillance populations to KQ 1 (diagnostic accuracy of biomarkers), and added initial diagnosis to KQ 6 (blue light cystoscopy).

Key Question 1: What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in 1) persons with signs or symptoms warranting evaluation for possible bladder cancer or 2) persons undergoing surveillance for previously treated bladder cancer?

     a) Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, ethnicity), or according to the nature of the presenting signs or symptoms?

Key Question 2: For patients with non-muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., Guidelines of the European Association of Urology or based on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need

for cystectomy, quality of life) compared with treatment not guided by an assessed risk-adapted approach?

Key Question 3: For patients with non-muscle-invasive bladder cancer treated with transurethral resection of bladder tumor (TURBT), what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with other agents, TURBT alone, or cystectomy?

    a) What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?
    b) Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?
    c) Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?
    d) Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities?

Key Question 4: For patients with high risk non-muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?

Key Question 5: In surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?

    a) Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?
    b) Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?
    c) Does the comparative effectiveness differ according to the length of surveillance intervals?
    d) Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or ethnicity?

Key Question 6: For initial diagnosis or surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?

Key Question 7: What are the comparative adverse effects of various tests for diagnosis

and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?

Key Question 8: What are the comparative adverse effects of various treatments for non-muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?

    a) How do adverse effects of treatment vary by patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?

PICOTS

Population(s)
Include:
- For KQ 1, 6, and 7: Adults with signs or symptoms of possible bladder cancer (e.g., gross or microscopic hematuria, irritative voiding symptoms)
- For KQ 2: Adults with non-muscle-invasive bladder cancer (stages Ta, Tis, or T1)
- For KQ 3 and 8: Adults with non-muscle invasive bladder cancer treated with TURBT
- For KQ 4 and 8: Adults with high-risk non-muscle invasive bladder cancer treated with TURBT
- For KQs 1 and 5 through 7: Adults undergoing surveillance following treatment for non-muscle invasive bladder cancer

Interventions
Include:
- For KQ 1, 5, and 7: Urinary biomarkers[a]
- For KQ 2: Risk-adapted treatment approaches
- For KQ 3a, 3b, 3c, 3d, and 8: Intravesical chemotherapeutic or immunotherapeutic agents[b]
- For KQ 4: External beam radiation therapy, with or without systemic chemotherapy or immunotherapy
- For KQ 6: Blue light or other methods of augmented cystoscopy

Comparators
Include:
- For KQ 1, 5, and 7: Other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)
- For KQ 2: Treatment not guided by risk-adapted approach
- For KQ 3a, 3b, 3c, 3d, and 8: Other intravesical chemotherapeutic or immunotherapeutic agent, different dose or duration of intravesical chemotherapy or immunotherapy, or transurethral resection of bladder tumor (TURBT) alone
- For KQ 4: Intravesical chemotherapeutic or immunotherapeutic agents or cystectomy

Outcomes

Include:

- For KQ 1 and 5: Diagnostic accuracy, using cystoscopy with biopsy as the reference standard
- For KQ 2, KQ 3, KQ 4, KQ 5: Mortality, disease-specific and all-cause
- For KQ 2, KQ 3, KQ 4, KQ 5: Need for cystectomy
- For KQ 2, KQ 3, KQ 4, KQ 5, KQ 6: Recurrence of cancer
- For KQ 2, KQ 3, KQ 4, KQ 5: Progression of cancer
- For KQ 2, KQ 3, KQ 4, KQ 5: Quality of life
- For KQ 7: Adverse effects of diagnostic testing (e.g., false-positives, labeling, anxiety, complications of cystoscopy)
- For KQ 8: Adverse effects of treatment (e.g., cystitis, urinary urgency, urinary frequency, incontinence, hematuria, pain, urosepsis, myelosuppression

Timing

Include:

- Any duration of follow-up
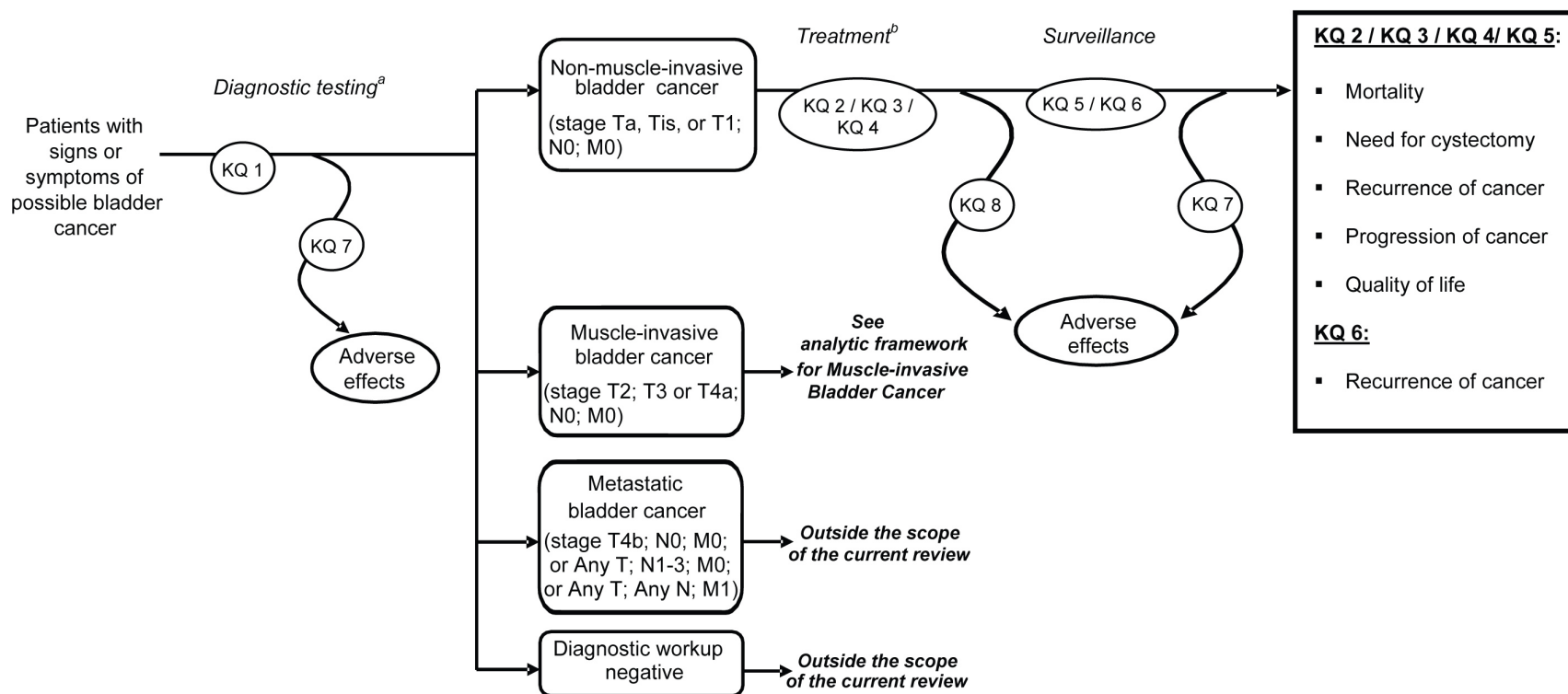
Settings

Include:

- Inpatient settings
- Outpatient settings

[a] Restricted to tests that are approved for diagnosis of bladder cancer by the U.S. Food and Drug Administration (BTAstat® [BTA], Alere NMP22®, BladderChek® [NMP22], UroVysion® [FISH] and ImmunoCyt™ [immunocytology]) or available in the U.S. and classified as a Laboratory Developed Test by the FDA (CxBladder™)

[b] Chemotherapeutic and immunotherapeutic agents of interest include: mitomycin; apaziquone; paclitaxel; gemcitabine; thiotepa; valrubicin; doxorubicin; bacillus Calmette-Guérin (BCG); and interferon.

III. Analytic Framework

Figure 1. Analytic framework for Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer.

[a] Urinary biomarkers of interest are restricted to tests that are approved for diagnosis of bladder cancer by the U.S. Food and Drug Administration (BTAstat[®] [BTA], Alere NMP22[®], BladderChek[®] [NMP22], UroVysion[®] [FISH] and ImmunoCyt[™] [immunocytology]) or available in the U.S. and classified as a Laboratory Developed Test by the FDA (CxBladder™)
[b] Chemotherapeutic and immunotherapeutic agents of interest include: mitomycin; apaziquone; paclitaxel; gemcitabine; thiotepa; valrubicin; doxorubicin; bacillus Calmette-Guérin (BCG); and interferon

IV. Methods

A. **Criteria for Inclusion/Exclusion of Studies in the Review** The criteria for inclusion and exclusion of studies will be based on the Key Questions and discussion with TEP members, and are described in the previous PICOTS section.

Below are additional details on the scope of this project:

Study Designs: For KQ1, KQ 3, KQ 4, KQ 6, KQ 7 and KQ 8 we will include randomized controlled trials (RCTs) and cohort studies with comparators if RCTs are not available. For KQ 2 and KQ 5, studies that report diagnostic accuracy will be included. For all KQs we will exclude uncontrolled observational studies, case-control studies, case series, and case reports, as these studies are less informative than studies with a control group.

Systematic reviews will be used as primary sources of evidence if they address a key question and are assessed as being at low risk of bias, according to the AMSTAR quality assessment tool.[12, 13] If systematic reviews are included, we will update findings with any new primary studies identified in our searches, update meta-analyses if appropriate, and re-assess SOE based on the totality of evidence. If multiple systematic reviews are relevant and low risk of bias, we will focus on the findings from the most recent reviews and evaluate areas of consistency across the reviews.[14, 15]

Outcomes: For KQ 1 and KQ 5, we will include studies that report the diagnostic accuracy of biomarkers for initial detection of bladder cancer or recurrence of bladder cancer and effects of using biomarkers on clinical outcomes such as mortality and disease progression. We will exclude studies of biomarkers for prediction of treatment response or disease progression. While identification of biomarkers for predicting treatment response and disease progression are important issues, this was determined to be out of the scope of this review.

Non-English Language Studies: We will restrict to English-language articles, but will review English language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, in order to assess for the likelihood of language bias.

B. **Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions** Publication Date Range: Searches will begin in January 1990, a date early enough to capture all relevant published studies of current treatments for bladder cancer.

Library searches will be updated while the draft report is posted for public comment and peer review to capture any new publications. Literature identified during the update search will be assessed by following the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the final submission of the report.

Literature Databases: Ovid MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment, National Health Sciences Economic Evaluation Database, and Database of Abstracts of Reviews of Effects will be searched to capture both published and grey literature. See Appendix A for the primary Ovid MEDLINE search strategy.

Scientific Information Packets:

Scientific information packets (SIPs) will be requested from drug and device manufacturers and a notice inviting submission of relevant scientific information will be published in the Federal Register in an effort to identify any relevant unpublished literature that may contribute to the body of evidence. All interested parties will have the opportunity to submit data for this review during a four-week period, using the AHRQ Effective Health Care publicly accessible online SIP portal (http://effectivehealthcare.ahrq.gov/index.cfm/submit-scientific-information-packets/).

Manufacturers of currently available and FDA approved diagnostic biomarkers for diagnosis and surveillance of bladder cancer, and treatments for Non-MIBC will be invited to provide SIPs.

Hand Searching: Reference lists of included articles will also be reviewed for includable literature. Searches will also be supplemented by suggestions from the TEP.

Contacting Authors: In the event that information regarding methods or results appears to be omitted from the published results of a study, or if we are aware of unpublished data, we will query the authors to obtain this information.

Process for Selecting Studies: The KQs and PICOTS described above will be used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide. To ensure accuracy, all excluded abstracts will be dual reviewed. All citations deemed appropriate for inclusion by at least one of the reviewers will be retrieved. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus.

C. **Data Abstraction and Data Management** After studies are selected for inclusion, data will be abstracted into categories that include but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics (age, sex, bladder cancer stage, performance status), intervention characteristics (drugs, dosage, duration), and results relevant to each key question as outlined in the previous PICOTS section. Information that will be abstracted that is relevant for assessing applicability will include the number of patients randomized relative to the number of patients enrolled, and characteristics of the population, intervention, and care settings. Sources of funding for all studies will also be recorded. All study data will be verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

D. **Assessment of Methodological Risk of Bias of Individual Studies** Predefined criteria will be used to assess the risk of bias for individual controlled trials, systematic reviews, and observational studies by using clearly defined templates and criteria as appropriate. Studies will be evaluated using appropriate criteria developed by the U.S. Preventive Services Task Force.[16] Systematic reviews will be assessed using the AMSTAR quality rating instrument.[13] These criteria and methods will be used in conjunction with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the AHRQ Methods Guide developed by the Agency for Healthcare Research and Quality.[12] Studies will be rated as "low risk of bias," "medium risk of bias," or "high risk of bias."[15, 17]

Studies rated "low risk of bias" will be considered to have the least risk of bias, and their results will be considered valid. "Low risk of bias" studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "medium risk of bias" will be susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of low risk of bias, but no flaw likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "medium risk of bias" category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some medium risk of bias studies are likely to be valid, while others may be only possibly valid.

Studies rated "high risk of bias" will have significant flaws that imply biases of various types that may invalidate the results. They will have a serious or "fatal" flaw or flaws in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. Studies with fatal flaws have one or more serious issues that introduce a high risk of bias as identified during assessment using the criteria outlined above.[16, 18] An example of a study with a fatal flaw would be a study with very high loss to follow up (e.g., >60%), failure to perform appropriate intention-to-treat analyses, and/or use of inadequate randomization procedures (e.g., alternating allocation). The results of these studies will be at least as likely to reflect flaws in the study design as the true difference between the compared interventions. We will not exclude studies rated as being high risk of bias a priori, but high risk of bias studies will be considered to be less reliable than low or medium risk of bias studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Each study evaluated will be independently reviewed for risk of bias by two team members. Any disagreements will be resolved by consensus.

E. **Data Synthesis** We will review and highlight studies by using a hierarchy-of-evidence approach, where the best evidence is the focus of our synthesis for each key question.

We will construct summary tables to highlight the main findings. Qualitative data will be summarized in summary tables and as ranges and descriptive analysis and interpretation of the results will be provided.

Meta-analyses will be conducted to summarize data and obtain more precise estimates on outcomes for which studies are homogeneous enough to provide a meaningful combined estimate. The feasibility of a quantitative synthesis will depend on the number and completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analysis could be meaningfully performed, we will consider the risk of bias for each of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes, and may conduct sensitivity analyses. Meta-regression may be conducted to explore statistical heterogeneity using additional variables on methodological or other characteristics (e.g., risk of bias, randomization or blinding, outcome definition and ascertainment) given enough number of studies.

Results will be presented as structured by the key questions, and any prioritized outcomes will be presented first.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes
The strength of evidence for each key question will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.[12] To ensure consistency and validity of the evaluation, the grades will be reviewed by the entire team of investigators for:
- Risk of bias (low, medium, or high risk of bias)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or undetected)

Assessments of reporting bias will be based on whether studies defined and reported primary outcomes, and when available, by comparing published results to results reported in trial registries. The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High — We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate — We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low — We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

- Insufficient — We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

G. **Assessing Applicability** Applicability will be estimated by examining the characteristics of the patient populations (e.g., demographic characteristics; stage of disease; performance status); interventions; the sample size of the studies; and settings (e.g., patients in developing countries) in which the studies are performed. Issues with applicability may limit the ability to generalize the results to other populations and settings.

V. References

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VI. Definition of Terms

- <u>Bladder Cancer</u>: Cancer that starts in the bladder, the part of the body that holds and releases urine.
- <u>Cystectomy</u>: Surgical removal of all or part of the urinary bladder.
- <u>Hematuria</u>: Blood in the urine.
- <u>Immunotherapy</u>: Treatment that induces, enhances, or suppresses the immune response in order to treat a disease (e.g., cancer).
- <u>Intravesical Therapy</u>: A drug (chemotherapy or immunotherapy) directly into the bladder through a catheter rather than giving it by mouth or injecting it into a vein.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Search Strategy

Primary Search Strategy (Ovid MEDLINE) for Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer *and* Treatment of Non-metastatic Muscle-invasive Bladder Cancer

1. exp Urinary Bladder Neoplasms/ (42649)
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (560)
3. (cis or Tis or ta or t1$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (171383)
4. 2 or 3 (171904)
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1411)
6. 4 or 5 (173181)
7. 1 and 6 (4066)
8. exp Biological Markers/ (599845)
9. 7 and 8 (577)
10. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (135002)
11. 7 and 10 (290)
12. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (348853)
13. exp Surgical Procedures, Operative/ (2324899)
14. exp Drug Therapy/ (1046457)
15. exp Antineoplastic Agents/ (806939)
16. exp Radiotherapy/ (134644)
17. (th or su or rt or dh or dt).fs. (4403551)
18. 13 or 14 or 15 or 16 or 17 (6203229)
19. 12 and 18 (143282)
20. 7 and 19 (165)

21. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (260287)

22. 7 and 21 (1034)

23. (electromotiv$ or emda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (438)

24. 1 and 23 (29)

25. (blue adj5 cystoscop$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (40)

26. 1 and 25 (30)

27. exp Radiotherapy/ (134644)

28. rt.fs. (153801)

29. 27 or 28 (215263)

30. 7 and 29 (231)

31. 9 or 11 or 20 or 22 or 24 or 26 or 30 (2005)

32. exp Urinary Bladder Neoplasms/ (42649)

33. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5934)

34. (t2$ or t3$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (92421)

35. 33 or 34 (97810)

36. 32 and 35 (4517)

37. cystectom$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (10382)

38. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1540)

39. 37 or 38 (11727)

40. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1201)

41. (avoid$ adj7 cystectom$).mp. (51)

42. 40 or 41 (1247)

43. exp Lymph Node Excision/ (34323)

44. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, abstract, original title, name of substance word, subject

heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (29000)

45. 43 or 44 (38668)

46. (adjuvant$ or neoadjuvant$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (146279)

47. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (181085)

48. 46 or 47 (308733)

49. 39 or 42 or 45 or 48 (350734)

50. 36 and 49 (2242)

51. 31 or 50 (3863)

52. limit 51 to yr="1990 -Current" (3413)

53. limit 52 to english language (2874)

54. limit 52 to abstracts (3288)

55. 53 or 54 (3408)