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The RAZOR (randomized open vs robotic cystectomy) trial: study design and trial update

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Abstract

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Conflict of Interest

D.A.B. reports personal fees from Janssen, GE Healthcare, outside the submitted work.
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The purpose of the RAZOR (randomized open vs robotic cystectomy) study is to compare open radical cystectomy (ORC) vs robot-assisted RC (RARC), pelvic lymph node dissection (PLND) and urinary diversion for oncological outcomes, complications and health-related quality of life (HRQL) measures with a primary endpoint of 2-year progression-free survival (PFS). RAZOR is a multi-institutional, randomized, non-inferior, phase III trial that will enrol at least 320 patients with T1–T4, N0–N1, M0 bladder cancer with ≈160 patients in both the RARC and ORC arms at 15 participating institutions. Data will be collected prospectively at each institution for cancer outcomes, complications of surgery and HRQL measures, and then submitted to trial data management services Cancer Research and Biostatistics (CRAB) for final analyses. To date, 306 patients have been randomized and accrual to the RAZOR trial is expected to conclude in 2014. In this study, we report the RAZOR trial experimental design, objectives, data safety, and monitoring, and accrual update. The RAZOR trial is a landmark study in urological oncology, randomizing T1–T4, N0–N1, M0 patients with bladder cancer to ORC vs RARC, PLND and urinary diversion. RAZOR is a multi-institutional, non-inferiority trial evaluating cancer outcomes, surgical complications and HRQL measures of ORC vs RARC with a primary endpoint of 2-year PFS. Full data from the RAZOR trial are not expected until 2016–2017.

Keywords

bladder cancer; cystectomy; robotics; clinical trials

Introduction

In 2012, ≈74 000 patients were diagnosed with urinary bladder cancer with nearly 15 000 estimated deaths from bladder cancer in the USA alone [1]. Radical cystectomy (RC) with pelvic lymphadenectomy (PLND) and urinary diversion is a standard of care for both high-risk, non-muscle-invasive bladder cancer and muscle-invasive disease [2,3]. This surgery is extremely complex and associated with considerable postoperative morbidity [4–6], with major and minor complications after open RC (ORC) of ≈13% and 67%, respectively [4,5]. Robot-assisted RC (RARC) is a less invasive technique with RC and PLND accomplished via a robot-assisted laparoscopic approach [7]. After completion of the RC and PLND, urinary diversion is performed by either extracorporeal or intracorporeal techniques. Potential advantages of RARC from small-volume, single-institution series are decreased estimated blood loss (EBL), decreased blood transfusion rates, diminished pain and opioid requirements, earlier time to oral intake, shorter hospital stay, fewer wound complications, and expedited perioperative and postoperative convalescence and recovery [8–10]. From a cancer perspective, RARC does not appear to compromise oncological outcomes defined by surgical margin status and number of pelvic lymph nodes removed in early robotic series [8–10].

Nix et al. [11] conducted a small (41 patients) prospective, randomized, single centre, trial of RARC vs ORC with a primary endpoint of lymph node yield. Significant differences were noted in operating room time, EBL, time to flatus and bowel movement, as well as use of inpatient morphine equivalents, without significant differences in complications or hospital

stay. The mean number of lymph nodes removed was 19 (RARC) vs 18 (ORC), demonstrating non-inferiority.

Parekh et al. [12] conducted a pilot, prospective randomized trial evaluating perioperative outcomes and oncological efficacy of RARC vs ORC in 40 consecutive patients with significantly decreased EBL and trends toward decreased length of stay of >5 days and fewer transfusions in the RARC group. There were no significant differences in positive margins or number of lymph nodes removed for RARC compared with ORC, although fewer lymph nodes were recovered via the robotic approach.

Nonetheless, RARC is still associated with significant complications. Johar et al. [13] described complications in 939 patients after RARC from the International Robotic Cystectomy Consortium database, with complications analysed and graded according to the Memorial Sloan-Kettering Cancer Center system. In all, 41% and 48% of patients had complications at ≤30 and ≤90 days of surgery, respectively. Nearly 20% of patients had a grade ≥3 complication after RARC and 90-day mortality was 4.2%. Yuh et al. [14] reported on 196 patients who underwent RARC, extended PLND, and urinary diversion, with continent diversions performed in 68% of cases. Complications at ≤90 days of surgery were defined and categorised by the modified Clavien system. In all, 80% of patients had a complication ≤90 days after surgery, and 35% had a major complication, with 90-day mortality of 4.1%. Thus, postoperative complications and morbidity after RARC are considerable but generally similar to contemporary ORC series.

RARC for bladder cancer has the potential for improving perioperative morbidity compared with ORC without compromise of oncological efficacy. Unfortunately, the vast majority of studies to date are retrospective with significant inherent selection bias. High levels of clinical evidence for the benefits of RARC are absent, and current experiences represent case series with limited comparisons to historical controls, or small, single-institution randomized clinical trials at best. Comparative results of RARC vs ORC clearly need validation in larger, multicentre, randomized, prospective clinical trials and this is certainly the goal of the RAZOR (randomized open vs robotic cystectomy) trial.

RAZOR Experimental Design

This multi-institutional, randomized, prospective, non-inferiority, phase III trial will enrol at least 320 patients with ≈160 in both the RARC and ORC arms at 15 participating institutions (Table 1). Thus far, 306 patients have been randomized to the RAZOR study from 19 August 2011 to the 19 December 2013: an average of ≈11 patients accrued per month, with expected completion of patient accrual in 2014. This study aims to determine whether RARC for treatment of bladder cancer provides non-inferior oncological control vs traditional ORC with a primary endpoint of 2-year progression-free survival (PFS). A multi-institutional approach with patients randomized to either approach having surgery performed by experienced surgeons should minimise both institutional and surgeon biases.

Patient Inclusion Criteria

Patients must have biopsy confirmed bladder cancer; clinical stages T1–T4, N0–N1, M0, or carcinoma *in situ* refractory to intravesical therapies. Review of the official pathology report at participating institutions is mandatory but central pathological review is not required.

Patient Exclusion Criteria

Inability to give informed consent, age of <18 or >99 years, and pregnancy are absolute exclusion criteria. In addition, at the discretion of the treating surgeon, previous major abdominal or pelvic surgical procedures precluding a safe robotic approach or any pre-existing condition, e.g. severe chronic obstructive pulmonary disease, precluding safe initiation or maintenance of pneumoperitoneum during surgery are also exclusion factors.

Research Procedures (Tables 2,3)

Any patient deemed a candidate for RARC will be offered participation in the study in attempts to eliminate selection bias. Eligible, consented patients are randomized to RARC or ORC no >60 days before surgery using a dynamic balancing algorithm on type of diversion, within each institution as a block via a web-based patient enrolment and randomization system through the data management services of Cancer Research and Biostatistics (CRAB). Surgeons performing RARC and/or ORC must have performed ≥10 each over the 1 year prior to approval as a study site. Within each study site, the open and robotic surgeon(s) could be more than one individual. All urinary diversions are extracorporeal with specific type selected by mutual agreement of the patient and surgeon. The extent of PLND (standard vs extended template) is also determined by the surgeon but at a minimum includes external iliac, obturator, and hypogastric regions. Standard and extended surgical templates were implemented for the study and adherence to these templates assessed by submission of a ‘Surgeon’s Intraoperative Data Form’ for all cases to CRAB.

Objectives of the RAZOR Trial

Oncological

The primary endpoint of the RAZOR trial is 2-year PFS, with stratification factors including type of urinary diversion, clinical stage and neoadjuvant chemotherapy. As a non-inferiority comparison, the study will test whether RARC is (at worst) inferior to ORC by a small pre-defined margin. For statistical power and significance, the margin for this trial is 15%, meaning RARC would be considered inferior if 2-year PFS is >15% lower than ORC. A total of 288 evaluable patients (144 patients per arm) yields 80% power and a two-sided significance level (α) of 5% to correctly reject the null-hypothesis of unacceptable inferiority of RARC. These calculations are based on assumptions that 2-year PFS in the patients receiving ORC is roughly 70% [2] and the rate of 2-year progression is binomially distributed. Concerning analysis of the primary endpoint, a one-sided Mantel–Haenszel test with half the α (0.025) will be used for testing the primary non-inferiority hypothesis comparing 2-year PFS between treatment arms. The study uses a centralised dynamic allocation procedure to allocate equal numbers of patients to each treatment arm and balance marginal distribution of stratification factors between treatment arms. Participation was

anticipated at 15 sites with estimated overall accrual of 110 eligible patients per year. Assuming a maximum drop-out rate of 10%, a total of at least 320 patients (160 in each arm) will be accrued over ≈3 years and followed for at least 2 years for disease progression. Based on accrual estimates, after 3 years of accrual and 2 additional years of follow-up, 65% of patients should have follow-up data available to evaluate PFS at 3 years. Thus, study duration is expected to be ≈5 years.

Of note, in superiority trials the intent-to-treat (ITT) population is widely accepted for analysis of the primary endpoint as it gives the most conservative result. In contrast, for non-inferiority trials the inclusion of ineligible or untreated patients, or lack of adherence to the assigned treatment is expected to increase background noise of the study and make the treatment arms look more alike, and thus the overall results of the study less conservative. RAZOR therefore uses the per-protocol (PP) population for analysis of the primary endpoint, as well as all efficacy and health-related quality of life (HRQL) endpoints. The PP population is a subset of the ITT population and includes all patients who met inclusion/exclusion criteria and received surgery. The ITT population includes all patients randomized to the trial, and a sensitivity analysis of the primary endpoint using the ITT population will also be performed. Trial design and analysis are based on Southwest Oncology Group (SWOG) standards for non-inferiority trials.

Patients will be followed from the date of surgery to the date of first documentation of progression of bladder cancer or death from any cause. Imaging of the chest, abdomen and pelvis will be performed at baseline and then again at 12, 24 and 36 months to assess for disease recurrence (Table 2). Acceptable modalities include chest X-ray, CT imaging of the chest, abdomen and pelvis, as well as MRI of the abdomen and pelvis, given patient factors and surgeon discretion. Although follow-up history, physical examination, laboratory and surveillance imaging schedules are uniform for the RAZOR trial (Table 2), some authors advocate a more individualised, risk-based surveillance strategy based on pathology at the time of RC [15]. Patients known to be alive and progression free are censored at date of last contact. Progression is determined using **R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors (RECIST) 1.1 criteria based on either radiographic or pathological evidence of disease progression, or death from disease. Any documented recurrence is considered progression. All patients will be followed for at least 2 years and an estimated 65% followed for 3 years. Overall survival (OS) is defined from date of surgery to date of death from any cause. Patients last known to be alive are censored at date of last contact. PFS and OS will be evaluated using the Kaplan–Meier method and comparisons between arms using the stratified log-rank test.

Laboratory

Serum haemoglobin and comprehensive metabolic panel (CMP) are part of routine preoperative evaluation and postoperative follow-up in patients undergoing RC and urinary diversion and are thus determined at baseline and in the postoperative period at 4–6 weeks, and at 3, 6, 12, 24, and 36 months. Linear mixed effects are used to compare blood level parameters and changes over time between the two treatment groups.

HRQL

HRQL outcomes are measured at baseline and postoperatively at 3 and 6 months using the Functional Assessment of Cancer Therapy–Vanderbilt Cystectomy Index (FACT-VCI) as well as the Short Form 8 (SF-8) questionnaires. Simple descriptive statistics, including mean and standard deviation (SD) are used to summarise FACT-VCI and SF-8 scores at each time point for each treatment group. A multivariate linear mixed effects model is fitted to each score in this repeated measures design. The main effect is visit (at baseline, 3 and 6 months) and treated as a categorical variable to accommodate for non-linear trends. If time corresponding to a particular visit differs significantly between patients, a variable representing deviation from the visit-specific mean time is added to the model. Standard diagnostic tools are used to assess model fit.

Several patient-reported and performance-related measures of functional independence are analysed as part of the RAZOR trial. Activities of Daily Living (ADL) and Instrumental ADL (IADL) scores are determined both at baseline and postoperatively at 4–6 weeks, and at 3 and 6 months. Hand Grip Strength Test and Timed Up and Go Walking Test outcomes are evaluated at baseline and postoperatively at 4–6 weeks, and at 3 and 6 months. Hand Grip Strength at 3 months after surgery is measured as a surrogate for recovery after surgery. Previous reports suggest only 39% of patients recovered at 3 months after a major abdominal surgery as measured by Hand Grip Strength [16].

RAZOR compares the proportion of patients recovered as measured by Hand Grip Strength between the two treatment arms. We hypothesise 20% more patients will have recovered 3 months after surgery in the RARC arm compared with the ORC arm. A total of 288 patients yield 91% power and a one-sided significance level of 0.025 to detect a difference between arms of at least 20%. These calculations are based on assumptions that Hand Grip Strength at 3 months is binomially distributed.

Operative

It is estimated nodal templates will be equivalent for RARC and ORC with minimal standard template PLND including all potential lymph node-bearing tissue with the lateral limit the genitofemoral nerve, distally Cooper’s ligament to include Cloquet’s node, proximally the crossing of the ureter over the common iliac vessels, medially the bladder including tissue medial to the hypogastric artery, posteriorly the floor of the obturator fossa with circumferential mobilisation of the external iliac artery and vein off the pelvic sidewall. Surrogates of surgical quality are compared by evaluating surgical margin status and number of lymph nodes removed. Surgical soft tissue margin as a measure for local cancer control is measured as positive or negative for each patient and compared between arms using a Fisher’s exact test. The number of nodes resected in each arm is compared using a *t*-test.

Pathological

The RC specimen (with or without uterus, ovaries, or vaginal cuff in females and prostate in males) is submitted *en bloc*, processed and assessed in a standardised fashion at all participating institutions for margin status along with histology, tumour size, stage, grade and presence/absence of lymphovascular invasion. At a minimum, lymph nodes are

submitted in two separate packets labelled left and right pelvic. All regions may be submitted in smaller packets (e.g. external iliac, obturator, internal iliac) at surgeon discretion. Pathological data is obtained from pathology reports after surgery with particular emphasis on surgical margin status, total number of lymph nodes removed and their involvement with cancer, as well as pathological stage of the tumour. A standardised form is used to collect all information pertaining to specimen processing and staging by the participating institutions, and the standardised 'Cystectomy Pathology Form' submitted to CRAB with a copy of the pathology report available in patients' clinical records.

Perioperative

Perioperative measures, e.g. EBL, blood transfusion rates, intraoperative fluid requirements, operative time, postoperative length of hospital stay and analgesic requirement, are prospectively recorded during surgery and the postoperative hospital stay using anaesthesia, operative, nursing and inpatient medical records by a research coordinator. All medications are converted to morphine equivalents using the online calculator, The Clinician's Ultimate Reference found at http://www.globalrph.com/narcoticonv.htm.

RAZOR will determine whether RARC is superior to ORC in terms of blood loss by comparing EBL between groups. A total of 288 patients yield 90% power and a one-sided significance level of 0.025 to detect a difference of blood loss between the two treatment groups of 20%. These calculations are based on assumptions that blood loss is normally distributed, and the mean (SD) EBL for ORC is 575 (300) mL. RAZOR will also determine whether RARC is superior to ORC in terms of transfusion rates. The transfusion rate for ORC is estimated at 75%. A total of 288 patients yield 92% power and a one-sided significance level of 0.025 to detect a difference in transfusion rates between arms of at least 20%. These calculations are based on the assumption that transfusion rate is binomially distributed.

Length of hospital stay is used as a surrogate for recovery after surgery. RAZOR will determine whether RARC is superior to ORC in terms of length of hospital stay. It is estimated all patients receiving ORC stay in the hospital for >5 days while 67% of patients undergoing RARC stay in the hospital for >5 days. A total of, 288 patients yield 97% power and a one-sided significance level of 0.025 to detect a difference in the percentage of patients requiring a hospital stay beyond 5 days between arms of at least 20%. These calculations are based on the assumption that the percentage of patients requiring a >5-day hospital stay is binomially distributed.

Morbidity

Perioperative morbidity and mortality are evaluated using the modified Clavien grading system for complications by prospectively recording intraoperative and postoperative complications until discharge and by patient interview during the post-discharge period until 90 days after surgery.

Cost

RAZOR compares fixed and variable costs associated with RARC and ORC operating room and hospital components. Fixed and variable operating room costs are assessed using amortised cost of the robot per case, amortised cost of robot maintenance per case, costs of dispensable equipment, cost of operating room personnel and anaesthesia resources per time. Fixed and variable hospital costs are obtained based on length of stay. Cost data is collected from each participating centre then stored and analysed by CRAB. We hypothesise that costs associated with RARC will be no more than 5% greater than ORC.

Data Safety and Monitoring (Table 4)

A Data and Safety Monitoring Committee (DSMC) will oversee the conduct of the study and consist of five voting, independent members: one surgeon, one medical oncologist, one Certified Clinical Research Associate (CCRA)/Registered Nurse (RN), one biostatistician, and one lay person. Non-voting members include support staff from CRAB (who will prepare the DSMC reports), and project faculty (Principal Investigators) as appropriate. DSMC members receive database summaries from CRAB, including adverse events (AEs) and post-surgical complications reports, serious AE (SAE) summaries, and other pertinent patient/treatment summary information. Meetings occur every 6 months via teleconference. The DSMC is responsible for decisions about possible termination and/or early reporting of the study.

Subject data is examined at each follow-up visit and subjects queried for AEs defined as complications related to RARC, ORC and/or study procedures. An AE or complication is the appearance of undesirable sign(s), symptom(s), or medical condition(s) occurring after a participant signs informed consent and considered to be related to RARC, ORC and/or study procedures. A SAE is any untoward medical occurrence that is fatal or life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in disability/incapacity, or is medically significant and may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. All AEs or complications will be graded for severity according to the modified Clavien grading system. All AEs will be reported to the Institutional Review Board (IRB) at the time of annual review and to the DSMC as described below.

Each investigator must assess the relationship between any study-related procedure and occurrence of each SAE. The investigator uses clinical judgment to determine the potential relationship. Alternative causes, such as natural history of underlying diseases, concomitant therapy, other risk factors, and temporal relationship of the event to any study-related procedure is considered and investigated. The investigator may change his/her opinion of causality in light of follow-up information and amend the SAE case report form and report accordingly. SAEs meeting the IRB definition of ‘Unanticipated Problems Involving Risk to Subjects or Others’ (UPIRSO) are reported to the IRB within 7 days, and within 48 h if life-threatening or fatal. All SAEs are also summarised and communicated across sites via posting to the secure study website at https://prodq.crab.org/Parekh/Login.aspx. Data are reviewed on a biweekly basis by investigators to ensure quality control and safety. During

the study, when there is a safety evaluation, the investigator and/or research staff are responsible for detecting, documenting and reporting AEs or SAEs to the local IRB.

Potential Limitations of the RAZOR Trial

Randomized surgical clinical trials are challenging for myriad reasons, and the RAZOR study is not immune to many of these challenges. Firstly, not all surgeons are created equal. Surgical talent and experience vary widely. However, Birkmeyer et al. [17,18] studied the relationship of surgeon and hospital volumes on mortality after RC and urinary diversion, and found both surgeon and hospital volumes were inversely related to perioperative mortality. All surgeons in the RAZOR trial would be categorised as high-volume surgeons from high-volume hospitals in these studies, thus minimising surgeon variability. Another potential limitation of the RAZOR trial is the learning curve of RARC and possibly comparing an established technique to a novel technique with many surgeons still on the learning curve. Surgeons performing RARC and/or ORC in the RAZOR study must have performed ≥10 each over the 1 year prior to approval as a study site in an effort to minimise the influence of the learning curve. In addition, if RARC is non-inferior to ORC for cancer control, the outcomes of RARC should only improve with more widespread dissemination of technique. Finally, the true impact of RARC on HRQL outcomes may be underestimated in the RAZOR trial due to use of extracorporeal urinary diversion. Although the primary endpoint of the RAZOR trial is oncological with HRQL a secondary measure, the full HRQL influence of RARC may perhaps only be realised with intracorporeal urinary diversion.

Conclusions

The RAZOR study is a landmark multi-institutional, prospective, non-inferiority trial evaluating oncological outcomes, surgical complications, and HRQL measures of ORC vs RARC in patients with T1–T4, N0–N1, M0 bladder cancer with a primary endpoint of 2-year PFS. Thus far, 306 patients have been randomized to the RAZOR study from 19 August 2011 to 19 December 2013: an average of ≈11 patients accrued per month, with expected completion of patient accrual in 2014. Full data from the RAZOR trial are not anticipated until 2016–2017 but should provide much needed level 1 data about the comparative efficacy of RARC vs ORC in terms of both cancer control and HRQL.

Abbreviations

(I)ADL	(Instrumental) Activities of Daily Living
(S)AE	(serious) adverse event
CRAB	Cancer Research and Biostatistics
DSMC	Data and Safety Monitoring Committee
EBL	estimated blood loss
FACT-VCI	Functional Assessment of Cancer Therapy–Vanderbilt Cystectomy Index

HRQL	health-related quality of life
IRB	Institutional Review Board
ITT	intent-to-treat (population)
(P)LND	pelvic lymphadenectomy
OS	overall survival
PFS	progression-free survival
PP	per-protocol (population)
RAZOR	randomized open vs robotic cystectomy(trial)
(O)(RA)RC	(open) (robot-assisted) radical cystectomy
SF-8	Short Form 8 (questionnaire)

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Table 1

Accrual of patients to date at the 15 participating institutions.

Institution	Accrual, *n*
Mayo Clinic, Arizona	50
Stanford University	40
University of Texas – San Antonio	34
University of Michigan	30
University of North Carolina	30
Mayo Clinic, Minnesota	21
University of Minnesota	20
University of Chicago	17
University of Virginia	13
University of Miami	13
Ohio State University	12
Vanderbilt University	9
University of California – Irvine	8
Loyola University – Chicago	8
Brigham and Women's Hospital	1
Total	**306**

Table 2

Study calendar for measurements of study endpoints.

Assessment	Baseline (preoperative)	Hospital discharge (±2 weeks)	Follow-up assessments					
			4–6 weeks	3 months	6 months	12 months	24 months	36 months
Baseline history and physical examination, consent, screening, ECOG performance status, TURBT findings	√							
Randomization	√(≤60 days before surgery)							
PFS						√	√	√
OS			√	√	√	√	√	√
ADL score	√		√(±30 days)	√(±30 days)	√(±30 days)			
IADL score	√		√(±30 days)	√(±30 days)	√(±30 days)			
Hand Grip Strength test	√		√(±30 days)	√(±30 days)	√(±30 days)			
Timed Up and Go Walking test	√		√(±30 days)	√(±30 days)	√(±30 days)			
Haemoglobin, BMP, serum albumin	√		√	√	√	√	√	√
HRQL questionnaire – FACT-VCI and SF-8	√			√(±30 days)	√(±30 days)			
Obtain pathology reports for surgical margin status and lymph node count			√					
Surgical complications per modified Clavien classification (AEs/SAEs)			√	√	√	√	√	√
Postoperative complication rates (Surgeon's 90-day Data Form)				√				
Imaging (CT/MRI of abdomen/pelvis/chest)	√					√	√	√
Operating room costs, Hospital costs		√						
Surgeon's intraoperative data, cystectomy, pathology		Postoperative						
Length of hospital stay, analgesics, complications (Surgeon's Postoperative Data Form)		√						
Target lesions (Post-Surgical Disease Assessment Form)					√	√	√	√

BMP, basic metabolic panel; ECOG, Eastern Cooperative Oncology Group.

Table 3

Data submission procedures. Data must be submitted according to the following schedule.

1.	Perform randomization and obtain subject identification number: Randomization Form.
2.	Within 1 week after enrolment: Medical History Form Surgical History Form Findings at TURBT Form Haemoglobin, BMP, and Serum Albumin Form Screening Physical Examination and Vital Signs Form Baseline Disease Assessment Form Baseline FACT-VCI HRQL Questionnaire Baseline SF-8 HRQL Questionnaire Baseline ADL HRQL Questionnaire Baseline IADL HRQL Questionnaire Baseline Hand Grip Strength Form Baseline Timed Up and Go Walking Test Form
3.	Within 1 week of surgery: Surgeon's Intraoperative Data Form
4.	Within 1 week of discharge for surgical hospitalisation: Hospital Discharge Visit: OR and Hospital Costs Reporting Form Surgeon's Postoperative Data Form
5.	Within 1 week of each post-surgery laboratory assessment: Haemoglobin, BMP, and Serum Albumin Form
6.	Within 1 week of each scheduled ADL, IADL, and HRQL assessment: FACT-VCI HRQL Questionnaire SF-8 HRQL Questionnaire ADL HRQL Questionnaire IADL HRQL Questionnaire Hand Grip Strength Form Timed Up and Go Walking Test Form
7.	Within 2 weeks of each scheduled disease assessment/imaging examination: Post-surgical Disease Assessment Form
8.	Within 4–6 weeks after surgery: Cystectomy Pathology Form
9.	Within 1 week following the 90-day postoperative period: Surgeon's 90-day Data Form
10.	Within 1 week of the 6-, 12-, 24-, and 36 months postoperative assessments (respectively): Post-surgical Disease Assessment Form Haematology Form Serum Chemistry Form

BMP, basic metabolic panel.

Table 4

AE submission procedures. Data about AEs must be submitted according to the following schedule.

1.	Within 1 week of each scheduled AEs evaluation until AEs have resolved: Surgical Complications-Adverse Events Form
2.	Within 7 days or 48 h if life-threatening for each SAE: Flag as 'SAE' on the Surgical Complications-Adverse Events Form
3.	Within 2 weeks of knowledge of death, if death occurs before the end of the study: Death Report Form