# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

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| **Title** | Provider Referral Patterns Following Nephrectomy in High-Risk Locoregional Renal Cell Carcinoma |
| **Protocol number** | A6181230 |
| **Protocol version identifier** | Final Version 4 (Amendment 1) |
| **Date** | 27 March 2020 |
| **Research question and objectives** | To estimate the proportion of patients diagnosed with locoregional renal cell carcinoma who are at high risk for recurrence following nephrectomy, describe referral patterns, and characterize treatment in this population. Outcomes including estimation of the incidence of recurrence and disease-free interval following nephrectomy will be reported overall and among the subgroup of patients receiving adjuvant systemic therapy with sunitinib following nephrectomy. |
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## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AEM | adverse event monitoring |
| AIC | Akaike information criteria |
| CI | confidence interval |
| DCF | data collection form |
| ECOG | Eastern Cooperative Oncology Group |
| EMR | electronic medical record |
| HCRU | health care resource utilization |
| IEC | independent ethics committee |
| IRB | institutional review board |
| KPS | Karnofsky Performance Scale |
| NIS | non-interventional study |
| OQA | RTI-HS Office of Quality Assurance |
| RCC | renal cell carcinoma |
| RTI | RTI International |
| RTI-HS | RTI Health Solutions |
| SSIGN | stage, size, grade, and necrosis (score) |
| TNM | tumor, node, metastasis (cancer staging system) |
| UISS | UCLA Integrated Staging System |
| US | United States |

## 3. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
| PPD PharmD, MSc | PPD | PPD | PPD |
| PPD | | | |
| PPD MD | PPD | | |
| PPD MS | Project Leader | PPD | |
| PPD PhD | Project Supervisor | PPD | |

## 4. ABSTRACT

**Provider Referral Patterns Following Nephrectomy in High-Risk Locoregional Renal Cell Carcinoma**

Version 4 (27 March 2020)

**Background and rationale:** In 2017, renal cell carcinoma (RCC) accounted for nearly 4% of new cancer cases in the United States. Among patients initially diagnosed with regional or distant disease, 5-year survival is 67% and 12%, respectively. Although only 16% of patients are initially diagnosed with regional disease, up to 40% will experience relapse with distant metastases following nephrectomy. The high rate of recurrence among these patients highlights a continued unmet need for effective adjuvant treatment that can reduce recurrence risk, prolong the disease-free interval, and/or improved overall survival.

Yet, it is unclear whether postnephrectomy patients in real-world practice settings are typically assessed for recurrence risk postoperatively and whether patients at high risk of recurrence are seen by providers who can evaluate candidacy for adjuvant therapy, clinical trials, or alternative surveillance schedules. Additional evidence is needed to understand referral patterns and follow-up care following nephrectomy for patients at high risk of recurrence. Results from this study may provide needed evidence to understand populations of patients who are at the greatest risk of disease recurrence and investigate possible areas of unmet surveillance and treatment needs.

**Objectives:** To estimate the proportion of patients diagnosed with locoregional RCC who are at high risk for recurrence following nephrectomy, describe referral patterns, and characterize treatment in this population. Exploratory analyses may include estimation of the incidence of recurrence and disease-free interval following nephrectomy, if data are available.

**Study design:** Non-interventional, retrospective medical record review of patients diagnosed with locoregional RCC who received a nephrectomy in Duke University's health system (Duke). Using a published algorithm (eg, the UCLA Integrated Staging System [UISS] or the stage, size, grade, and necrosis [SSIGN] score) or adaptation of a published algorithm, patients at high risk of recurrence following surgery will be followed until the end of their patient record, death, or disease recurrence to examine referral patterns, receipt of systemic therapy, disease recurrence, and death. The study will consist of a pilot phase to test the data abstraction tool and determine feasibility of assessing the study objectives with available data and a full abstraction phase to compile the necessary data, conduct the analyses, and generate the documents for dissemination of the study results.

**Population:** Patients aged 18 years or older who were diagnosed with locoregional RCC and underwent nephrectomy at Duke between 01 April 2014 and 31 December 2019. The final date range for patient inclusion was determined after the part 2 data collection was complete.

**Variables:** Background (eg, age at nephrectomy, sex) and baseline clinical characteristics (eg, performance status, TNM [tumor, node, metastasis] stage, histology, tumor grade, categorical risk of recurrence following nephrectomy by commonly used clinical nomograms); postnephrectomy treatment and referrals; and disease recurrence events and survival will be assessed, where available.

**Data sources:** Duke researchers will abstract the necessary information from the electronic medical records of eligible patients and enter deidentified information into the study database. This study is retrospective; therefore, the collection of data will in no way influence prescribing patterns or treatment decisions.

**Study size:** Data will be abstracted from a target of 20 eligible patients during the pilot phase. During full abstraction, data for approximately 650 patients will be targeted for abstraction.

**Data analysis:** Descriptive summary of baseline characteristics by UISS risk categories among patients with locoregional RCC. Among patients at high risk of recurrence, descriptive summary of postnephrectomy follow-up care. Time-to-event outcomes (eg, disease-free interval) will be described using the Kaplan-Meier method, if feasible.

**Milestones:** Key milestones include finalization of the protocol (December 2018), finalization of the data-collection form (January 2019), completion of ethics submission (January 2019), completion of pilot phase and finalization of feasibility memo (June 2019), start of data collection (July 2019), completion of part 2 data collection (September 2019), completion of part 2 data analysis (November 2019), and finalization of the part 2 study report (December 2019). Additional key milestones relevant to the expanded data collection include finalization of the updated protocol (Q1 2020), completion of ethics submission (Q1 2020), start of expanded data collection (Q2 2020), completion of expanded data collection (Q2 2020), completion of expanded data analysis (Q2 2020), and finalization of the updated study report (Q3 2020).

# 5. AMENDMENTS AND UPDATES

| Amendment Number | Date | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
|---|---|---|---|---|
| 1 | 11 June 2019 | 9.1. Study design<br>9.2.1. Inclusion criteria | The study period is now 01 April 2014 to 31 March 2019. | The study period has been updated to reflect the most recent 5-year period available in the data. The pilot phase feasibility study demonstrated that a 5-year period is more than sufficient to achieve the minimum desired sample size of 500 eligible patients. |
| 2 | 27 March 2020 | Section 4 and Section 9<br>Section 4 and Section 9<br>Section 4 and Section 6 | Update date ranges throughout to reflect a study period through 31 December 2019.<br>Increase the number of patient records abstracted to 650.<br>Update study timeline and milestones. | The new Common Rule does not require dates for retrospective studies. Updating the date limitation will allow for nephrectomies from 2019 to be collected and for follow-up to extend through the most recent medical record entry for previously identified patients.<br>Increase the number of subjects to include patients who have had more recent nephrectomies (up to 650 total). |

## 6. ANTICIPATED MILESTONES

| Milestone | Planned Date |
|---|---|
| Final protocol | 18 Dec 2018 |
| Submit IRB applications | 18 Jan 2019 |
| Feasibility assessment (pilot phase) | 05 Jun 2019 |
| Start of full data collection | 01 Jul 2019 |
| End of full data collection | 15 Sep 2019 |
| Final analytic results | 11 Dec 2019 |
| Final study report | 31 Dec 2019 |
| Final updated protocol | Q1 2020 |
| Submit revised IRB application | Q1 2020 |
| Start expanded data collection | Q2 2020 |
| End expanded data collection | Q2 2020 |
| Final updated analytic results | Q2 2020 |
| Final updated study report | Q3 2020 |

IRB = institutional review board.

## 7. RATIONALE AND BACKGROUND

In the United States (US), renal cell carcinoma (RCC) accounts for nearly 4% of new cancer cases and resulted in an estimated 14,400 deaths in 2017 (National Cancer Institute, 2018).[11] Five-year survival for patients with RCC is 74%; however, prognosis varies by disease stage. Among patients initially diagnosed with regional or distant disease, 5-year survival is 67% and 12%, respectively.

Nephrectomy is the recommended treatment for most patients with localized or regional disease, followed by surveillance (Motzer et al., 2017).[10] Although only 16% of patients are initially diagnosed with regional disease, up to 40% will experience relapse with distant metastases following nephrectomy (Janzen et al., 2003; Breda et al., 2007).[6,2] The high rate of recurrence among these patients highlights a continued unmet need for effective adjuvant treatment that can reduce recurrence risk, prolong the disease-free interval, and/or improve overall survival.

Yet, it is unclear whether postnephrectomy patients in real-world practice settings are typically assessed for recurrence risk postoperatively and whether patients at high risk of recurrence are seen by providers who can evaluate candidacy for adjuvant therapy, clinical trials, or alternative surveillance schedules. Additional evidence is needed to understand postoperative referral patterns and follow-up care for patients at high risk of recurrence.

In this study, researchers at Duke University's School of Medicine and Health System (Duke) and RTI Health Solutions (RTI-HS) will collaborate on a non-interventional, retrospective medical record review study aimed at examining postnephrectomy referral patterns and treatment characteristics in patients diagnosed with RCC. The feasibility of estimating disease recurrence and disease-free interval following nephrectomy in this population will also be explored. Results from this study may provide needed evidence to understand the proportion of postnephrectomy patients who are at the greatest risk of disease recurrence and investigate possible areas of unmet surveillance and treatment needs.

## 8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to estimate the proportion of patients diagnosed with RCC who are at high risk for recurrence following nephrectomy, describe referral patterns, and characterize treatment in this population. Exploratory analyses may include estimation of the incidence of recurrence and disease-free interval following nephrectomy, if data are available. Data for this study will be collected from a retrospective medical record review of patients diagnosed with locoregional RCC who underwent nephrectomy at Duke. The following primary objectives will be assessed:

- Describe patient demographic and clinical characteristics of patients diagnosed with locoregional RCC who underwent nephrectomy.
- Estimate the proportion of patients at high risk of recurrence following nephrectomy.

- Characterize postoperative provider referrals among patients at high risk of recurrence, including the proportion of patients who were referred to other providers and reasons for referral.

- Describe treatment characteristics following nephrectomy among patients at high risk of recurrence, including the proportion of patients who received systemic therapy, type of systemic therapy received, dose and duration of treatment, reasons for treatment discontinuation, and participation in clinical trials, where available; perform subgroup analyses to describe treatment details among the subgroup of patients receiving adjuvant systemic therapy with sunitinib.

- Estimate the incidence of disease recurrence and duration of the disease-free interval following nephrectomy among all patients at high risk of recurrence, and among the subgroup of patients receiving adjuvant systemic therapy with sunitinib.

## 9. RESEARCH METHODS

To achieve the study objectives, retrospective medical record data of adult patients diagnosed with locoregional RCC who received a nephrectomy at Duke will be compiled by Duke researchers and analyzed by RTI Health Solutions (RTI-HS) analysts. RTI-HS will develop a customized data-collection form (DCF) to capture detailed information on patient demographics, clinical characteristics, health outcomes, treatments, and postoperative referrals from the medical records of eligible patients. Patients will be selected based on specific inclusion and exclusion criteria described in Sections 9.2.1 and 9.2.2. All necessary study materials will be submitted to Duke's institutional review board (IRB) for review and RTI International's[1] IRB for study classification.

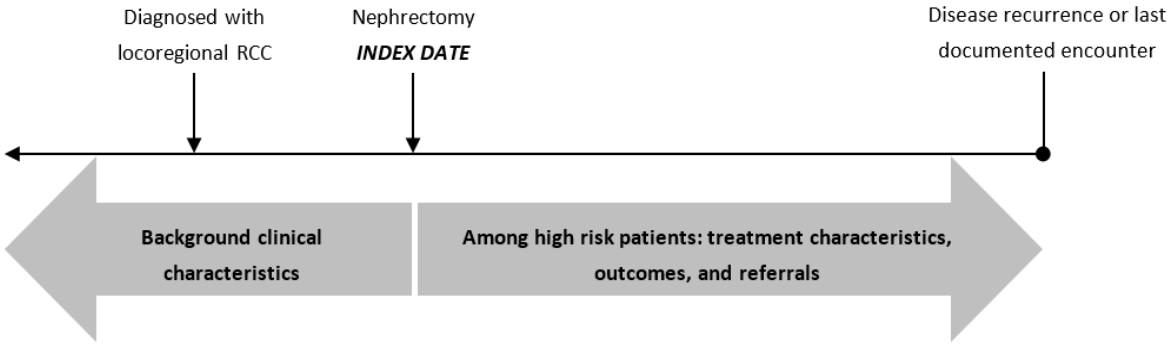
Following receipt of each IRB's classification or approval of the study (where required), Duke researchers will proceed with implementation of the pilot study (pilot phase). The pilot phase will consist of a pilot study to assess whether an adequate sample of the patient population of interest is available, evaluate the quality and completeness of available data, and quantify the duration of follow-up care available in Duke's electronic medical record (EMR) system. Using lessons learned from the pilot study, part 2 (the full study) will consist of abstracting data for a large sample of patients, analyzing the data, and preparing a study report and other materials for disseminating the study findings (ie, conference abstract, poster, and manuscript). Based on the temporal trends observed in part 2, the data abstraction will be expanded to include part 3 (the expanded study), which will consist of abstracting data on the additional patients who underwent nephrectomy through 2019 and expanded follow-up data collection (ie, referral patterns, treatment patterns, and outcomes) for previously identified patients at high risk of recurrence, to include follow-up dates through the most recent available medical record entry prior to the abstraction date.

[1] RTI Health Solutions is a business unit of the not-for-profit research organization RTI International.

## 9.1. Study Design

This study is a retrospective, observational medical record review of patients diagnosed with locoregional RCC who received a nephrectomy at Duke between 01 April 2014 and 31 December 2019. The date of the nephrectomy will be considered the *index date*. Background clinical characteristics such as date of initial and locoregional RCC diagnoses will be identified during the period prior to the index date. Recurrence risk status will be assigned at the index date, using information available in the record at or around the index date. During the follow-up period (ie, the period between the index date and the last entry in the medical record, death, or disease recurrence), outcomes including treatment, referrals, and disease recurrence will be assessed for patients who were determined to have been at high risk of recurrence following their nephrectomy, where data are available. Figure 1 provides a visual schematic of relevant observation periods.

**Figure 1. Patient Observation Periods**




RCC = renal cell carcinoma.

### 9.1.1. Pilot Phase

To enable assessment of appropriate inclusion criteria and data availability, researchers will conduct an initial pilot study. Duke researchers have compiled a preliminary list of patients diagnosed with RCC who underwent nephrectomy between 01 November 2012, and 31 October 2018, using DEDUCE, Duke's EPIC query tool. A total of 1,069 patients were identified, of which approximately 75% (n = 801) are expected to have been diagnosed with locoregional disease. A total of 883 patients were identified between 01 November 2013, and 31 October 2018 (approximately 662 anticipated to have locoregional disease). At this time, the researchers anticipate that a total sample of approximately 500 patients diagnosed with locoregional RCC who underwent nephrectomy will be required to obtain a sample of 75 to 100 patients considered to have been at high risk for disease recurrence after surgery.

Based on these preliminary counts, it is likely that inclusion of nephrectomies occurring between 01 November 2013, and 31 October 2018, will generate a sufficient sample. Duke researchers will determine preliminary annual aggregated counts, which RTI-HS will use to estimate the anticipated sample size of patients at high risk of recurrence, based on a published algorithm (eg, UCLA Integrated Staging System [UISS] risk status or stage, size,

grade, and necrosis [SSIGN] score) and proportions identified in published literature. Assessing potential sample size during the pilot study will allow researchers to determine whether the proposed sampling strategy (ie, selecting nephrectomy between 01 November 2013, and 31 October 2018) is adequate to obtain the desired sample size. If it is not, nephrectomies occurring from 01 November 2012, may be considered.

After the updated preliminary count is established and the study is approved by Duke's IRB, Duke researchers will evaluate the quality and completeness of available data by abstracting data for at least 20 eligible patients by reviewing patient medical records from a random sample of 50 patients identified by the DEDUCE query tool. This process will determine the proportion of eligible patients in the broader patient list identified by DEDUCE, and whether adequate information required to meet the study objectives are regularly available in the medical record. Results of the pilot study will be used to inform the final sample size expectation and refine study objectives, as needed. Note that a full assessment of data availability is dependent on abstraction of one or more patients that are classified as being at high risk of recurrence. If the first 20 eligible patients abstracted do not include a patient that is classified as high risk, additional patients will be included in batches of five until data for at least one patient at high risk of recurrence have been abstracted.

### 9.1.2. Part 2: Full Study

Results from the pilot phase feasibility assessment validated the sample size assumptions, with 83% of nephrectomies identified in the DEDUCE query confirmed eligible for the study and 15% of eligible nephrectomies classified as high risk. This indicates that the minimum sample of 500 patients, with 75-100 high risk, will likely be exceeded. Nephrectomies between 01 April 2014 and 31 March 2019 will be included to ensure the most up-to-date patient sample.

Part 2 will consist of abstracting data for the full sample of eligible patients, analyzing the data, and reporting the results. Duke researchers will abstract data on the remaining sample of eligible patients. Baseline demographic and clinical characteristics will be abstracted for the anticipated sample of 500 patients. Of patients who are determined to be at high risk of recurrence following nephrectomy (anticipated sample of 75-100 patients), additional data on treatment characteristics, outcomes, and referrals will be abstracted.

Once the data are fully abstracted, anonymized patient-level data will be transferred to RTI-HS for analysis. All programming will be conducted using SAS statistical software (version 9.4 or higher). The analysis will be descriptive, with exploratory models to examine possible factors associated with disease recurrence and disease-free interval, if the sample size is sufficient.

### 9.1.3. Part 3: Expanded Data Collection

Results from the part 2 study indicated that referral and treatment patterns show an increasing trend from 2018 into 2019. To further capture this trend, an additional sample of all patients with nephrectomies occurring through 31 December 2019 will be abstracted. The additional sample size during this period is estimated to be approximately 115-150 patients, for a full

combined sample of up to 650 patients in total. In addition, expanded follow-up data (ie, referral patterns, treatment patterns, and outcomes) will be collected for previously identified patients at high risk of recurrence, to include follow-up dates through the most recent available medical record entry prior to the abstraction date.

## 9.2. Setting

Data will be abstracted from the Duke EMR system. Patients whose data will be included in the study will have met the criteria described in Sections 9.2.1 and 9.2.2. Refer to Figure 1 for a depiction of the follow-up period. No minimum follow-up time will be required. Outcomes among patients who are determined to be at high risk of recurrence will be observed over each patient's follow-up period—from the date of nephrectomy to death, disease recurrence, or the last date in their medical record (whichever occurs first).

### 9.2.1. Inclusion Criteria

Patients must meet *all* of the following inclusion criteria to be eligible for data abstraction:

- Diagnosed with locoregional RCC (no distant metastasis at the time of diagnosis).
- Underwent a nephrectomy at Duke between 01 April 2014, and 31 December 2019 (final dates determined based on results from part 2 data collection).
- Aged 18 years or older at nephrectomy.

### 9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

## 9.3. Variables

All variables will be gathered using the DCF developed by RTI-HS and described in Section 9.6.7. In the following sections, we describe the key analysis variables and study measures that will be gathered directly through the DCF or constructed during analysis. Limited data will be collected on all eligible patients with locoregional RCC nephrectomy, while additional variables will be collected for patients who are classified as having a high risk of recurrence (anticipated to be 15%-20% of the total population; see Section 9.5 for details).

A small portion of patients may undergo more than one nephrectomy during the study period (anticipated to be 5%-10% of the total population). For these patients, all data will be collected in reference to the highest risk eligible tumor.

Exact dates will be collected in the DCF but will not be retained in the analytic file or transferred from Duke to RTI-HS. See Section 10 for a description of the method for anonymizing date data.

### 9.3.1. Patient Characteristics (all eligible study patients)

Demographic characteristics available in patient medical records will be documented. The following characteristics will be included:

- Year of birth;
- Age at nephrectomy;
- Sex;
- Race and/or ethnicity.

### 9.3.2. Baseline Clinical Characteristics (all eligible study patients)

A number of clinical characteristics related to the initial diagnosis of locoregional RCC and nephrectomy will be collected. The following characteristics may be included (when available):

- Date of diagnosis of locoregional RCC;
- Date of nephrectomy;
- TNM [tumor, node, metastasis] stage;
- Tumor grade;
    - Fuhrman grade (I-IV);
- Tumor histology;
    - Clear cell predominant versus not clear cell predominant;
- Tumor size (cm);
- Tumor necrosis (present/absent);
- Partial versus radical nephrectomy;
- Performance status--ECOG (Eastern Cooperative Oncology Group); if a KPS (Karnofsky Performance Scale) score is abstracted, it will be converted to an ECOG score (https://oncologypro.esmo.org/Oncology-in-Practice/Practice-Tools/Performance-Scales).

### 9.3.3. Follow-up Visits (all eligible study patients)

Information about the first postoperative visit following nephrectomy will be collected for all eligible patients, when available, and any decisions regarding follow-up plans made at this visit will be documented.

- Date of first postoperative follow-up visit;
- Follow-up plan determined at first postoperative visit:
  - Surveillance;
  - Adjuvant systemic therapy;
  - Transfer of care to a non-Duke provider;
  - Follow-up plan not recorded in the medical record.

### 9.3.4. Referral Patterns (high-risk subgroup only)

Information on provider referrals for oncologic or RCC-related care will be collected only for patients at high risk of recurrence, when available.

- Dates of referral for oncologic/RCC-related care;
- Reasons for referrals for oncologic/RCC-related care;
- Referring provider type;
- Type of provider referred to;
- No documented referral for oncologic/RCC-related care.

### 9.3.5. Treatment Patterns (high-risk subgroup only)

Detailed information on treatment patterns will be collected only for patients at high risk of recurrence, when available. Note that for patients participating in a competitor clinical trial, detailed information on the specific agent used will not be collected.

- Dates of subsequent surgery, procedures, and adjuvant systemic therapy;
- Type and dose of systemic agents received;
- Participation in clinical trials.

### 9.3.6. Outcomes (high-risk subgroup only)

Health outcomes will be collected only for patients at high risk of recurrence, when available.

- Date of last follow-up encounter in the medical record;
- Date of death;
- Date of disease recurrence and method of confirmation;
- Type of disease recurrence (eg, locoregional versus distant, if applicable);
- Reasons for treatment discontinuation.

### 9.4. Data Sources

Data will be abstracted from medical records of patients receiving care within the Duke University Health System. This study is retrospective; therefore, the collection of data will in no way influence prescribing patterns or treatment decisions.

Medical record abstractions provide a unique opportunity to collect and analyze real-world data outside the highly controlled setting of clinical trials. Generally, medical record abstraction enables collection of detailed information on patient demographic and clinical characteristics, treatment patterns, health outcomes, and health care resource utilization (HCRU) that may otherwise be unavailable in a standardized manner. The use of medical record abstraction allows for the development of a highly customized DCF that meets the specific needs of this study.

Following ethics approval, the DCF will be programmed into an Excel-based data-collection instrument. The use of an Excel-based tool not only enables streamlined abstraction but also real-time consistency checks to improve the accuracy of the recorded data. Upon finalization of the DCF, physicians at Duke will proceed with data-collection activities. Physicians will screen their patients' records to identify eligible patients. Physicians will be responsible for selecting patient medical records that meet the inclusion and exclusion criteria described in Section 9.2. After the physician identifies an eligible medical record, he or she will complete the DCF for the patient by retrospectively reviewing all available data in the medical record. The use of physicians to directly abstract patient medical record data eliminates interviewer or abstractor bias. Additionally, physicians are able to quickly and accurately interpret notes contained within a patient record, thereby providing additional information from a qualitative source. See Section 9.9 for a detailed review of the strengths and limitations of this study type.

### 9.5. Study Size

The total sample size will reflect the total number of eligible patients undergoing nephrectomy at Duke University Health System during the study period. At this time, it is estimated that this will be approximately 650 patients. Of this broader sample, it is anticipated that approximately 15%-20%, or 98-130 patients, will be classified as at high risk of recurrence and eligible for additional data collection to document treatment patterns and outcomes. As this study is exploratory in nature, no formal power calculations were conducted to determine the sample size for this study. Furthermore, this study does not

involve formal hypothesis testing and is primarily being conducted to understand clinical characteristics, treatment patterns, and health outcomes. Any significance testing will be exploratory in nature. Thus, the sample size considered for this study should be adequate to address the study objectives.

### 9.6. Data Management

RTI-HS will perform the analyses described in this proposal using a SAS statistical software application housed on RTI-HS's secure, large-capacity, high-performance Linux mainframe. Experienced RTI-HS programmers and analysts will perform all analyses. To ensure the integrity and quality of the study results, we will follow our programming validation life-cycle process for all analyses. This includes quality-checking programs, logs, and output for accuracy according to relevant standard operating procedures.

To ensure the integrity and quality of study results, RTI-HS implements several practice standards for statistical programming, database management, and documentation for all projects involving databases analyses. The following three steps will be undertaken to achieve this high level of quality:

- Documentation of SAS programming;
- Validation of SAS programs;
- Database storage and retention.

#### 9.6.1. Documentation of SAS Programming

To ensure smooth transitions of analytic methods and work among programmers, reviewers, and other project personnel, documentation of the following information will be created for each SAS program:

- Project name;
- Program name;
- Program purpose;
- Program author;
- Date the program was completed;
- Descriptions of subsequent changes and/or enhancements, with name of programmer and date for each.

This information will be incorporated into each program in the form of a header. In addition to documenting this information in a general program header, each program will include

detailed comments throughout to describe the purpose and method of specific programming statements.

### 9.6.2. Validation of SAS Programs

In this section, we describe a variety of programming validation methods, including log review, review of data listings, and independent programming, which will be used to ensure that our SAS programs function as intended. The validation methods described in this section are not exhaustive, and additional measures will be implemented as appropriate.

### 9.6.3. Log Review

Programmers will review all SAS log files. This procedure is a widely accepted, basic level of program validation. The following issues must be addressed as part of a log review:

- No errors should appear in a log file.
- If warning messages or messages related to uninitialized variables are permitted in the log file, the programmer will document why they are permitted.
- The programmer will account for the number of observations reported at each executed data step, especially when the number of observations increases or decreases.
- The log file will contain all lines of the program as it was saved at the time of execution, and it will contain only those lines of code.

### 9.6.4. Review of Data Listings and Tables of Summary Statistics

Because an error-free log file does not necessarily demonstrate that a SAS program has functioned as intended, programmers will produce cell frequencies, means, and other summary statistics on specific data items to demonstrate that the program results are valid. Where appropriate, we also will have a separate analyst review these listings independent of the programmer.

### 9.6.5. Independent Programming

For highly complex programming tasks, a second programmer will attempt (if necessary) to independently reproduce output generated by the initial programmer. If the outputs are equivalent, the test will be considered successful. If the outputs are not equivalent, the programmers will evaluate the differences and make appropriate corrections.

### 9.6.6. Validation Documentation

For each SAS program used to produce final study outputs for presentation, RTI-HS will complete and store a formal SAS validation document.

### 9.6.7. Data-collection Form

As used in this protocol, the term DCF should be understood to refer to either a paper form or an electronic data record or both, depending on the data-collection method used in this study.

A DCF is required and should be completed for each included patient. The completed original DCFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives (ie, RTI-HS) of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the DCFs are securely stored at the study site *in* encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCF and any other data-collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

The source documents are the patient medical records; data collected on the DCFs must match those records.

### 9.6.8. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, DCFs and hospital records), copies of all DCFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the study agreement, whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 3 years after completion or discontinuation of the study, as expressed in separate contractual agreements between Duke University, RTI-HS, and Pfizer.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

RTI-HS and Duke will store in a secure location all copies of the original data files, as applicable. Data files stored on CD, DVD, or other media will be kept in a locked storage unit. Original data files will be housed on dedicated project space on RTI-HS' Linux server.

To ensure the integrity of the original files, they will be stored on the Linux server in a designated folder that cannot be overwritten. Data sets derived from the original files during the data-cleaning process will be stored in a separate folder.

### 9.7. Data Analysis

All variables described in Section 9.3 will be summarized descriptively through the tabular display of mean values, 95% confidence intervals (CIs), medians, quartiles, and standard deviations of continuous variables of interest and frequency distributions for categorical variables. All open-ended text fields associated with the "other" answer option will be evaluated and described, as appropriate.

All study-eligible patients will be included in descriptive analyses of variables pertaining to patient characteristics, baseline clinical characteristics, and initial postoperative follow-up visits (see Sections 9.3.1, 9.3.2, and 9.3.3 for details). Patients who are categorized as having a high risk of recurrence will be included in additional analyses described below. Risk classification will be assessed using published algorithms (eg, UISS and SSIGN score) or adaptation of a published algorithm. The primary risk classification system used to designate the high-risk subgroup for this study will be chosen based on completeness of data available in the patient medical records. Completeness will be assessed during the pilot study. If data are available to support more than one classification system, the UISS risk classification will be used. If some data are not available to support classification using a published algorithm, an adapted version of an algorithm will be explored.

Additional descriptive analyses performed within the high-risk subgroup will include referral patterns, treatment patterns, and health outcomes (see Sections 9.3.4, 9.3.5, 9.3.6). In addition to descriptive analyses, time-to-event measures (ie, time to recurrence, overall survival) will be assessed. To adjust time-to-event measures, a Kaplan-Meier method that accounts for right-censoring will be implemented (Klein and Moeschberger, 2005).[7] To evaluate time to recurrence, the endpoint will be programmed with the date of recurrence or date of death, whichever occurs first, as an eligible event; if neither of these events occurred, the outcome will be right censored at the date of the last medical record follow-up. To evaluate overall survival, the endpoint will be programmed with the date of death as an eligible event or right censored at the date of the last medical record follow-up.

Exploratory semiparametric Cox proportional hazards models will be used to evaluate factors associated with time to recurrence and overall survival. These outcomes will be defined as described previously. Separate models will be estimated for time to recurrence and overall survival. The models will take the following general form:

$$h(t) = h0(t)\ \exp(\beta_1 DEMOGRAPHIC_i + \beta_2 CLINICAL_i), \text{ (Equation 2)}$$

Where the following apply:

- h(t) will be the hazard function of recurrence and overall survival as a function of explanatory variables.

- h0(t) will be the baseline hazard of recurrence and overall survival.
- DEMOGRAPHIC will be a vector of patient demographic characteristics, including but not limited to the following:
  - Age;
  - Sex.
- CLINICAL will be a vector of underlying clinical characteristics, including but not limited to the following:
  - Tumor histology;
  - Type and duration of systemic treatment;
  - Referral status;
  - Subsequent procedures.

The independent variables included in the final Cox proportional hazard models will be selected through an iterative process. First, separate univariate models assessing the relationship between each potential independent variable (eg, tumor histology) and the time-to-event outcome (ie, recurrence and overall survival) will be fit (Klein and Moeschberger, 2005).[7] The model with the lowest Akaike information criteria (AIC) will be selected for further evaluation. Next, each unselected variable will be added independently to the previously selected model to determine whether the addition of the specific variable results in a lower AIC. The model with the lowest AIC will be selected for further evaluation. This process will be repeated with each of the remaining unselected variables until the addition of unselected variables no longer lowers the AIC. The most parsimonious model will have the lowest AIC. Additionally, variables of clinical significance may be included in the model. The overall goodness-of-fit of the final model will be assessed using Cox-Snell residuals and the proportional hazards assumption for the final set of covariates (Klein and Moeschberger, 2005).[7]

Cox proportional hazards models will generate a hazard ratio for each of the covariates included in the model, indicating the higher or lower rate of an event (relative to a reference category) at any given point in time following nephrectomy. Like odds ratios from a logistic model, a hazard ratio less than 1 indicates a lower rate of an event, while a ratio greater than 1 indicates a higher rate of an event, relative to a reference category.

### 9.8. Quality Control

The DCF will be designed to perform data checks for illogical or unusual data (eg, treatment starting prior to diagnosis) during data collection, so that such errors may be immediately corrected by the physician.

RTI-HS and its staff strive to meet the highest standards of professional performance and continuously improve our products and services. To ensure quality, we work with our clients to define requirements and clarify expectations, and we pledge that our products and services will comply with these requirements, meet or exceed client expectations, and deliver exceptional value.

The RTI-HS Office of Quality Assurance (OQA) is an independent unit that reports to the Vice President of RTI-HS and provides training on applicable regulations and guidelines, implements and maintains a series of standard operating procedures, and provides quality assurance monitoring for compliance with regulatory requirements.

RTI-HS will work closely with the selected subcontractors to establish and ensure a complete integration of procedures for the project. The OQA will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation. Audits are conducted by the OQA according to established criteria in standard operating procedures and other applicable procedures. The OQA reports quality assurance observations to the Project Director and facilitates corrective actions, if necessary.

### 9.9. Limitations of the Research Methods

Retrospective medical record reviews are subject to the following general limitations:

- Patients selected for study inclusion represent a sample of patients who received treatment at Duke. Therefore, study findings may not be generalizable to the overall population of patients with locoregional RCC or physicians who treat this disease in the US.

- All data captured in the DCF will be limited to information available in the patients' medical records held by Duke University. Information on health care services received outside the physician's care setting that is not recorded in the medical record will be unavailable for this study (eg, treatment received through a non-Duke urologist or other health care provider [eg, medical oncologist]).

- Data will be entered directly by the Duke research team and may be subject to entry errors and resulting inaccuracies in reporting. Although data checks will be in place to improve internal consistency of the data, responses will not be validated against the patients' medical records by an independent reviewer.

### 9.10. Other Aspects

Not applicable.

## 10. PROTECTION OF HUMAN SUBJECTS

Patient medical record data may contain highly sensitive and private personal health information. Therefore, the following data-collection strategies will be implemented to

ensure that the data collected in this study strictly comply with definitions of deidentified or anonymous data:

- At any point in this study, only the study team at Duke will have access to the patient's medical record data containing identifiable information. The non-Duke study team (ie, RTI-HS and Pfizer) will only have access to the abstracted data.

- The DCF will be programmed to calculate and retain the age at nephrectomy, rounded down to the integer year level, and the year of nephrectomy in the analytic file that will be transferred to RTI-HS for analysis. For example, the Duke researcher will enter a patient's exact date of nephrectomy and exact date of birth into the DCF. The DCF will internally calculate the number of days between the two dates (ie, date of nephrectomy minus the date of birth) and retain only the date difference, in integer years, and the year of nephrectomy in the analytic file.

- Exact dates relevant to study endpoints will be collected in the DCF but will not be retained in the analytic file or transferred from Duke to RTI-HS. The DCF will internally calculate the number of days between two dates (ie, study endpoint date minus the index date/date of nephrectomy) and retain only the date difference, in days, in the analytic file.

All study data transferred outside of Duke will be coded as a limited data set. This does not allow for the sharing of exact dates or other identifiers (such as name, medical record numbers, etc.). The risk of a breach of confidentiality is primarily from malicious system hacking in the presence of suboptimal network security in the case of electronic data collection. Outside of network security risks, identification of a single patient by members of the research investigative team, based on a combination of limited demographic information and treatment information, would require (in addition to malicious intent) access to all medical records and an extraordinary analytic effort, except, perhaps, in the case of exceedingly rare conditions, which the current study does not include. Based on the study design and data-collection procedures, the study team believes there is only a minimal/remote risk of identification of patients.

As stated previously, to protect the rights and freedoms of natural persons with regard to the processing of personal data, no protected health information will be collected, and thereby, no data containing patient identifiable information will be transferred to Pfizer.

## 10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The data will be stored at the study site on a secure server and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate

technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the study agreement and applicable privacy laws.

### 10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

### 10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

### 10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research.

This study will be conducted in accordance with the standards for retrospective studies in the US. Information describing the deidentified nature of the data will be submitted to RTI's IRB committee for review, requesting classification as a "non-interventional, not human data" study. If the IRB classifies the study as such, no additional reviews will be required.

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a health care provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the DCF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, sex, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female…" or "An elderly male…" Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators).*"

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

All necessary trainings for Duke and RTI-HS project staff will be coordinated by RTI-HS.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

## 13. REFERENCES

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## 14. LIST OF TABLES

None.

## 15. LIST OF FIGURES



## ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

## ANNEX 3. ADDITIONAL INFORMATION

Not applicable.