NONINTERVENTIONAL (NI) STUDY PROTOCOL

Title	A Retrospective Medical Record Review of First-Line Sunitinib Administration Schedules and Outcomes Among Patients with Metastatic Renal Cell Carcinoma in Latin America
Protocol number	A6181231
Protocol version identifier	V1
Date	13 June 2019
Research question and objectives	To describe real-world demographic and clinical characteristics, treatment characteristics, and clinical outcomes (eg, adverse events, progression-free survival) among patients in Latin America who were treated with first-line sunitinib for metastatic renal cell carcinoma and switched from the 4/2 to 2/1 administration schedule. In Brazil, an additional sample of patients who initiated sunitinib on the 2/1 schedule will be analyzed.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica
ANVISA	Agência Nacional de Vigilância Sanitária
CEISH	Ethics Committee of Human Research
CENDEISSS	Centro de Desarrollo Estratégico e Información en Salud y Seguridad Social
CI	confidence interval
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios
COMBIOETICA	La Comisión Nacional de Bioética
CONEP	Comissão Nacional de Ética em Pesquisa
CONIS	Consejo Nacional de Investigación en Salud
CRF	case report form
DCF	data collection form
DCT	data collection tool
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ERB	ethical review board
GPP	Good Pharmacoepidemiology Practices
HR	hazard ratio
IEC	independent ethics committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
INVIMA	Instituto Nacional de Vigilância de Medicamentos y Alimentos
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MSKCC	Memorial Sloan Kettering Cancer Center
NIS	noninterventional study
OQA	Office of Quality Assurance
PFS	progression-free survival
PI	principal investigator
Q	quarter
RAINBOW	RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity

Abbreviation	Definition
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
PPD	PPD
SAS	Statistical Analysis Software
STAR-TOR	Registry For Temsirolimus, Sunitinib, And Axitinib Treated Patients With Metastatic Renal Cell Carcinoma (mRCC), Mantle Cell Lymphoma (MCL), And Gastro-Intestinal Stroma Tumor (GIST)
TBD	to be determined

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

A Retrospective Medical Record Review of First-Line Sunitinib Administration Schedules and Outcomes Amogn Patients with Metastatic Renal Cell Carcinoma in Latin America

Version 1

Background: Over the past decade, targeted therapies have yielded significant improvement in the clinical outcomes of patients with metastatic renal cell carcinoma (RCC), leading to international guidelines for standard first-line treatment with sunitinib, bevacizumab + interferon, or pazopanib for patients with good or intermediate prognoses.[1] The standard administration schedule for sunitinib as first-line treatment for metastatic RCC is 50 mg per day for 4 weeks followed by 2 weeks off (ie, a 4/2 schedule). However, recent studies suggest that a schedule modified to 2 weeks of sunitinib followed by 1 week off (ie, a 2/1 schedule) improves tolerability with comparable outcomes.[2-5] A change to the schedule may result in fewer Grade 3 or Grade 4 toxicities and increased treatment duration.[5-9]

Rationale: Despite the potential benefit from a modified treatment schedule evidenced in several studies among patients in the United States and Europe, real-world clinical outcomes among patients who have switched from the 4/2 to the 2/1 schedule for metastatic RCC in Latin America are unexplored. The current study will provide a description of demographic and clinical characteristics, sunitinib treatment patterns, and associated adverse events (AEs) and outcomes among adult patients in Latin America who were diagnosed with metastatic RCC and who received first-line sunitinib on the 4/2 schedule and then switched to the 2/1 schedule. In Brazil, feasibility assessments indicate many physicians start patients on the 2/1 schedule upon initiation of sunitinib for metastatic RCC. To reflect the patient population in Brazil, a second sample of patients who initiated first-line sunitinib on the 2/1 schedule will be collected and analyzed separately.

Primary Objectives:

1. Describe demographic and clinical characteristics of patients in Latin America diagnosed with metastatic RCC who received first-line sunitinib and switched from the 4/2 to the 2/1 schedule.
2. Characterize detailed first-line sunitinib treatment patterns, including dose, schedule, total duration of sunitinib treatment, duration on the 4/2 schedule, duration on the 2/1 schedule, reasons for stopping treatment lines, and supportive care.

Secondary Objectives:

1. Explore clinical outcomes after switching to the 2/1 schedule, including response to treatment, AEs, progression-free survival (PFS), and overall survival.
2. Describe demographic, clinical and treatment characteristics (eg, duration of treatment, reasons for stopping treatment), and clinical outcomes (eg, treatment response, AEs, PFS, and overall survival) among patients in Brazil who initiated first-line sunitinib treatment for metastatic RCC on the 2/1 schedule.

Study Design: Noninterventional, retrospective medical record review of patients with metastatic RCC who received first-line treatment with sunitinib and switched from the 4/2 to 2/1 administration schedule. A second sample of patients who initiated first-line treatment with sunitinb on the 2/1 schedule in Brazil will be collected and analyzed separately.

Population: Patients diagnosed with metastatic RCC with clear cell histology who switched from a 4/2 schedule to a 2/1 schedule of sunitinib in first-line metastatic treatment between January 1, 2014 and June 30, 2018. Patients must be aged 18 years or older at the time of the switch. The final dates defining this selection period will be dependent on country-specific ethics and reporting requirements. A second sample of adults who initiated first-line treatment with sunitinb on the 2/1 between January 1, 2014 and June 30, 2018 in Brazil will be collected and analyzed separately.

Variables: Patient characteristics, clinical characteristics, first-line treatment patterns, treatment-related outcomes, AEs, and survival.

Data Sources: Information will be abstracted from patients' medical records and compiled into an anonymized analytic database. All abstracted information will be retrospective.

Study Size: Data will be abstracted from a target of at least 150 medical records of patients treated at various sites across 7 Latin American countries.

Data Analysis: Analyses will include a descriptive summary of patient characteristics, first-line treatment patterns (eg, time to switch from 4/2 to 2/1; 4/2, 4/1, and total treatment durations), first-line disease progression from the start of 4/2 and the start of 2/1 schedules, AEs, and survival from the start of 4/2 and the start of 2/1 schedules. Time-to-event outcomes (ie, overall survival, treatment duration, PFS) will be described using the Kaplan-Meier method. Patients who initiated treatment on the 2/1 schedule will be analyzed separately from patients who switched from the 4/2 to 2/1 schedule.

Milestones: Key milestones include finalization of the protocol and case report form (quarter [Q]2 2019), initiation of site feasibility assessments (Q1 2019), initiation of the ethics review process (Q2 2019), start of data collection (to be determined; following completion of ethics review on a site-by-site basis), final interim analysis (Q3/Q4 2019), and final analytic results and final study report (to be determined based on site contracting timelines).

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Initiate feasibility assessment with sites after sites complete the confidentiality agreement with PPD	Q1 2019
Finalize study materials	Q2 2019
Initiate ethics review process after PPD contracts with a participating site	Q2 2019
Start of data collection	TBD (following completion of ethics review on a site-by-site basis)
Final interim analysis	Q3/Q4 2019
Final analytic results	TBD (based on site contracting timelines)
Final study report	TBD (based on site contracting timelines)

TBD = to be determined; Q = quarter; PPD .

6. RATIONALE AND BACKGROUND

Worldwide, kidney cancer is the ninth most commonly diagnosed cancer, with approximately 338,000 new cases diagnosed in 2012.[10] In Latin America and the Caribbean, the incidence of kidney cancer is 2.5 and 4.7 per 100,000 females and males, respectively, which is slightly lower than the global incidence.[11] However, regional cancer registry data indicate a greater incidence per 100,000 in many Central and South American countries including Uruguay (females, 5.7; males, 13.4), Chile (females, 5.6; males, 10.4), Argentina (females, 4.5; males, 10.4), and Brazil (females, 3.0; males, 5.8).[12] Although kidney cancer also refers to cancers affecting the renal pelvis and ureter, which are typically transitional (urothelial) cell carcinomas, renal cell carcinoma (RCC) makes up approximately 80% of all kidney cancers.[1]

RCC is a highly vascularized solid tumor and angiogenesis is linked to proliferation and propensity for metastasis.[13-15] Over the past decade, targeted therapies, specifically angiogenesis inhibitors, have yielded significant improvement in the clinical outcomes of patients with metastatic RCC, leading to international guidelines for standard first-line treatment with sunitinib, bevacizumab + interferon, or pazopanib for patients with good or intermediate prognoses.[1]

The standard administration schedule for sunitinib as first-line treatment for metastatic RCC is 50 mg per day (oral dose) for 4 weeks followed by 2 weeks off (ie, a 4/2 schedule). In this scheme, sunitinib demonstrated a greater median overall survival over interferon alpha (26.4 vs. 21.8 months, respectively; hazard ratio [HR] = 0.821; 95% confidence interval [CI], 0.673 to 1.001; $P = 0.051$).[16] Median progression-free survival (PFS) was significantly longer in the sunitinib group (11 months) compared with the interferon alpha group (5 months) ($P < 0.001$). Yet, sunitinib-related Grade 3 adverse events (AEs) such as hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%) were observed. The dose intensity of sunitinib must be maintained for disease control. Higher exposure has been linked to better treatment response, extended time to progression, and overall survival.[17] However, treatment-related adverse events can lead to reductions in dose or dose interruptions, which in turn may lead to impaired quality of life and poorer outcomes as dosing is not maintainted.[17,18] The optimal treatment approach for maintaining sunitinib dosing while mitigating adverse events is unknown.[2]

Recent studies suggest that a schedule modified to 2 weeks of sunitinib followed by 1 week off (ie, a 2/1 schedule) improves tolerability with comparable outcomes.[2-5] A change to the schedule may result in fewer Grade 3 or Grade 4 toxicities and increased treatment duration.[5-8] In the RAINBOW study, researchers evaluated safety and efficacy of the 2/1 schedule among patients receiving sunitinib for metastatic RCC in multiple centers in Europe. Findings indicated patients who switched from the 4/2 to the 2/1 schedule experienced a favorable safety profile compared to the prevalence and frequency of adverse events occurring during the initial 4/2 schedule.[7] A single site study of patients receiving first-line sunitinib also observed fewer toxicities among patients on the 2/1 schedule compared to those on the 4/2 schedule and comparable objective response rates and overall survival between the 2 groups.[3] The STAR-TOR study, a large German registry containing patients who receive sunitinib for

metastatic RCC (among other patients), reported similar adverse event mitigation with the 2/1 schedule and treatment duration more than three times longer than those who received the 4/2 schedule.[6] Longer duration translates to longer dose maintenance, which improves clinical outcomes.

Despite the potential benefit from a modified treatment schedule evidenced in studies among patients in the United States and Europe, real-world clinical outcomes among patients receiving the 2/1 schedule for metastatic RCC in Latin America are unexplored.[5-9] Further research on current, real-world clinical outcomes in this population may assist in providing additional context on the types of patients who may benefit from this alternative schedule.

The aim of the present study is to describe clinical characteristics, treatment patterns, and clinical outcomes (eg, PFS, change in prevalence of AEs) of adult patients with metastatic RCC in Latin America who received first-line sunitinib on the 4/2 schedule and then switched to the 2/1 schedule. In Brazil, feasibility assessments indicate many physicians start patients on the 2/1 schedule upon initiation of sunitinib for metastatic RCC. To reflect the patient population in Brazil, a second sample of patients who initiated first-line sunitinib on the 2/1 schedule will be collected and analyzed separately. As patient characteristics, prescribing patterns, health care systems, and access to care in community practice settings differ from highly controlled clinical trial environments, clinical outcomes (eg, treatment response, PFS, overall survival) in real-world patient populations may vary from published trials. As current research on health outcomes among patients who received sunitinib on a 2/1 schedule for metastatic RCC in these countries is absent, there is a lack in understanding as to whether the alternative treatment schedule is safe and effective in patients in Latin America.

Results from this study may aid in the following:

- Understanding characteristics of patients who switched from a 4/2 to a 2/1 sunitinib schedule or initiated the 2/1 schedule in Brazil, and the resulting clinical outcomes in the real-world setting.
- Describing the occurrence of AEs on the 4/2 and 2/1 schedules.
- Providing real-world, baseline measures of contemporary prescribing patterns and health outcomes to which future innovations in therapy could be compared.

7. RESEARCH QUESTION AND OBJECTIVES

This study consists of compiling and analyzing recent data from a customized retrospective medical record review conducted in 7 countries (Argentina, Brazil, Colombia, Costa Rica, Ecuador, Mexico, and Peru) to assess the following primary objectives:

- Describe demographic and clinical characteristics of patients in Latin America diagnosed with metastatic RCC who received first-line sunitinib and switched from the 4/2 to the 2/1 schedule.

- Characterize detailed first-line sunitinib treatment patterns, including dose, schedule, total duration of sunitinib treatment, duration on the 4/2 schedule, duration on the 2/1 schedule, reasons for stopping treatment lines, and supportive care.

The secondary objectives of the study will include an exploration of clinical outcomes (ie, response to treatment, AEs, PFS, and overall survival) after switching to the 2/1 schedule. Switching to the 2/1 schedule is a relatively new occurrence in the studied countries, resulting in limited available follow-up time to observe clinical outcomes among patients who switched to the alternative schedule. Furthermore, this study relies on a convenience sample of sites treating patients at a select number of treatment centers, will provide only descriptive information on observed events, and is designed to generate, not test, hypotheses. In Brazil, early feasibility results suggest physicians frequently prescribe sunitinib on the 2/1 schedule at first-line initiation; therefore, secondary objectives will also include a descriptive exploration of demographic, clinical and treatment characteristics (eg, duration of treatment, reasons for stopping treatment), and clnical outcomes (eg, treatment response, AEs, PFS, and overall survival) among patients initiating first-line sunitinib on the 2/1 schedule. It is anticipated this sample will be relatively small. Secondary objectives will be assessed with known limitations concerning data availability and generalizability of the findings.

8. RESEARCH METHODS

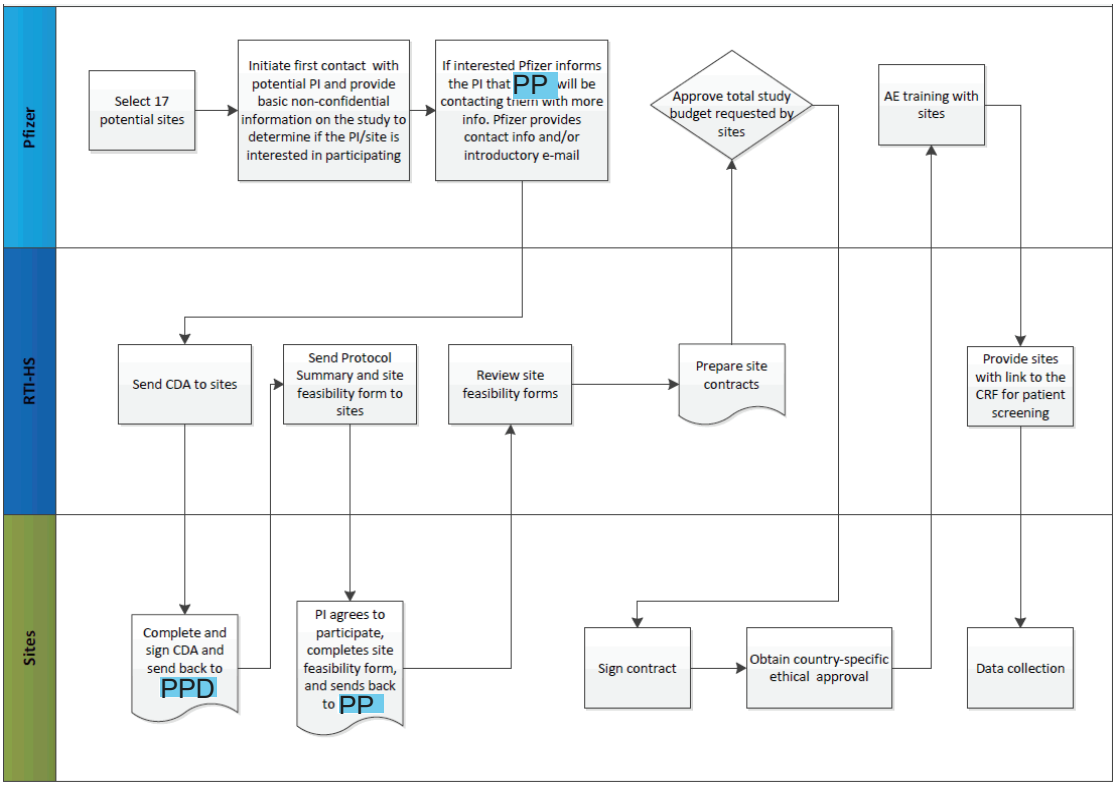
To achieve the study objectives described in Section 7 , PPD , a research consultancy specializing in conducting multinational real-world health economic and outcomes studies, will analyze retrospective medical record data from 150 patients who received care at treatment centers across 7 Latin American countries. Prior to initiation of data collection activities, PPD , in consultation with Pfizer Inc. (Pfizer), will develop a customized case report form (CRF) to capture detailed data on demographics, clinical characteristics, treatment patterns, AEs, and health outcomes from eligible patients' medical records. The length of the CRF will be consistent with an abstraction time burden of approximately 30 to 45 minutes. After selection of potential sites by Pfizer, PPD will work with the sites to assess feasibility of the site's participation by using a site information form. If the study is determined to be feasible at a specific site, the principal investigator (PI) and their designated research team at the participating site will obtain the necessary ethics approvals for conducting this study. In countries where national ethics activities are required, a lead site in the relevant country will be selected to support the national

submission. Specific responsibilities to be conducted and coordinated by Pfizer, PPD, and individual sites during the site identification, feasibility assessment, contracting process, and data collection are shown in Figure 1.

Following receipt of the required ethics approvals, the site PI and/or designated research team will be provided a link(s) to the secure electronic CRF (eCRF) to enter the abstracted data electronically. The PI may personally abstract data and/or designate their research team to abstract data. Once a potential medical record is identified, the abstractor will answer multiple screening questions in the eCRF to confirm the selected medical record is eligible for inclusion. Next, the abstractor will complete the eCRF by retrospectively reviewing all available data in the patient's medical record.

During the data collection phase, PPD will monitor recruitment and data collection activities. Upon completion of data collection, PPD will perform the analyses required to address Pfizer's study objectives. One interim analysis on partial data may be conducted upon Pfizer's request. Finally, PPD, in consultation with Pfizer, will develop a study report presenting the study methods, the CRF, the study results in the form of relevant tables and figures, and an interpretation of the results.

Figure 1. Site Selection, Feasibility Assessment, Contracting, and Data Collection Responsibilities



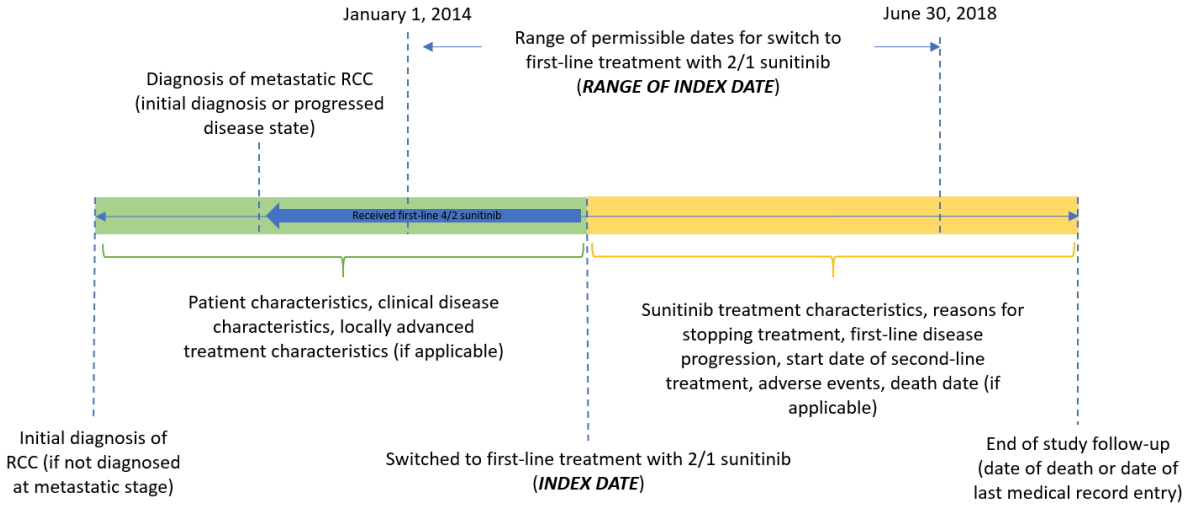
AE = adverse event; CDA = confidential disclosure agreement; CRF = case report form; PI = principal investigator; PPD.

8.1. Study Design

This study is a retrospective, observational medical record review of adult patients with metastatic RCC. A sample of 150 records of patients who meet the eligibility criteria described in Section 8.2.1 will be targeted. Data describing patient and clinical characteristics, first-line treatment patterns, AEs, and clinical outcomes will be abstracted directly by the PI and/or their designated research team. This study is descriptive, with the primary goal of retrospectively summarizing existing sunitinib treatment patterns and patient outcomes. As the data collected will be retrospective, the conduct of this study will in no way influence prescribed treatment. Figure 2 presents a graphical summary of the study design for patients who switched from the 4/2 to 2/1 schedule. Figure 3 displays a summary of the study design for the sample of patients in Brazil who initiated first-line sunitinib on the 2/1 schedule.

The primary measures of interest are described in Section 8.3.

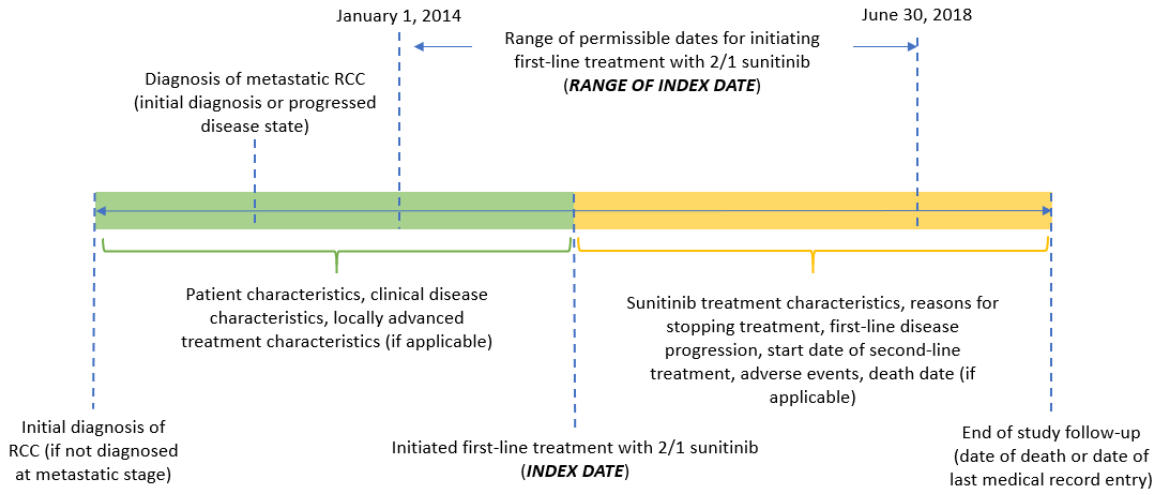
Figure 2. Study Design: First-Line Switch From 4/2 to 2/1 Sunitinib



RCC = renal cell carcinoma.

Note: The end of study follow-up may be contingent on country-specific or site-specific ethics requirements, for example, the last date of available data on the date of ethics approval at a given site. Patients may have a gap between stopping the 4/2 schedule and starting the 2/1 schedule.

Figure 3. Study Design: Initiated First-Line 2/1 Sunitinib (Brazil Only)



RCC = renal cell carcinoma.

Note: The end of study follow-up may be contingent on country-specific or site-specific ethics requirements, for example, the last date of available data on the date of ethics approval at a given site.

8.2. Setting

Data for this study will be abstracted from the medical records of patients treated for metastatic RCC at approximately 17 treatment centers (ie, sites) in 7 countries: Argentina, Brazil, Colombia, Costa Rica, Ecuador, Mexico, and Peru.

8.2.1. Patient Inclusion Criteria

1. Diagnosed with metastatic RCC with clear cell histology:

    a. The patient may have been initially diagnosed with Stage IV or initially diagnosed at an earlier stage and progressed to having disease at distant sites (ie, metastatic disease).

2. Initiated first-line treatment for metastatic RCC with sunitinib on the 4/2 schedule (all countries) or initiated first-line treatment for metastatic RCC with sunitinib on the 2/1 schedule (Brazil only).

3. Switched to the 2/1 schedule (all countries) or initiated the 2/1 schedule (Brazil only) during the first treatment line between January 1, 2014, and June 30, 2018:

    a. The final dates defining this selection period will be dependent on country-specific ethics and reporting requirements.

4. Aged 18 years or older at the time of the switch to the 2/1 schedule (all countries) or initiation of the 2/1 schedule (Brazil only).

8.2.2. Exclusion Criteria

1. Evidence of other malignant neoplasms (except nonmelanoma skin cancer or carcinoma in situ) within 5 years before switching to the sunitinib 2/1 schedule (all countries) or initiation of the 2/1 schedule (Brazil only).

8.3. Variables

All measures/variables will be gathered from existing medical records using the eCRF. In the following sections, we describe the key analysis variables and study measures that will be gathered directly through the eCRF or constructed during analysis.

8.3.1. Patient Characteristics

Demographic characteristics available in patients' medical records will be documented, including, but not limited to, the following (when available):

- Sex;
- Year of birth;
- Primary health insurance type (eg, supplemental private insurance, uninsured), if relevant;
- Comorbidities (eg, hypertension, diabetes);
- Height;
- Weight;
- Body mass index.

8.3.2. Baseline Clinical Characteristics

A number of clinical characteristics related to the initial RCC diagnosis and diagnosis of metastatic RCC will be collected. These characteristics may include, but are not limited to, the following (when available):

- Dates of diagnosis of initial (if first diagnosed at an earlier stage) and metastatic RCC;
- Stage of RCC at the time of initial diagnosis;
- Tumor grade at the time of initial diagnosis;

- Risk group at the time of initial diagnosis (eg, Memorial Sloan Kettering Cancer Center [MSKCC], International Metastatic Renal Cell Carcinoma Database Consortium [IMDC]);

- Site(s) of distant metastases at the time of initiation of first-line treatment with sunitinib and at the switch;

- Performance status (eg, Eastern Cooperative Oncology Group [ECOG], Karnofsky Performance Status Scale) at the time of initiation of first-line treatment with sunitinib and at the switch.

8.3.3. Treatment Patterns

Measures related to the treatment of RCC before (if applicable) and after diagnosis of metastatic RCC will be gathered. Figure 2 graphically depicts the time periods during which treatment patterns will be assessed for each sample. Treatment measures may include the following:

- Receipt of broad categories of treatment approaches, including neoadjuvant treatment(s), surgery, and adjuvant therapy before the diagnosis of metastatic RCC:
    - Date of receipt of last cancer-direct treatment before the diagnosis of metastatic RCC.
- Total number of systemic lines of treatment after the diagnosis of metastatic RCC:
    - Start and stop dates of each treatment line (duration of each treatment line will be calculated).
- Specific details regarding first-line treatment with sunitinib after the diagnosis of metastatic RCC include the following (where relevant to the specific sample):
    - Start and stop dates of the 4/2 schedule (duration of 4/2 treatment);
    - Date of switch to or initiation of the 2/1 schedule and stop date (duration of 2/1 treatment);
    - Time between stopping the 4/2 schedule and initiating the 2/1 schedule;
    - Reason for switch to 2/1 schedule;
    - Date of subsequent changes in schedule, if any
    - Reason for subsequent changes in schedule, if any
    - Initial and subsequent daily dose(s) of sunitinib on the 4/2 and 2/1 schedules:
        - Date(s) of dose change(s), if applicable;

    - Reason for change(s) in dose, if applicable.
  - Reason for stopping treatment with sunitinib (eg, AE, progressive disease);
  - Best clinician assessed response to treatment with sunitinib on the 4/2 schedule and best response on the 2/1 schedule.
- Receipt of broad categories of supportive care elements (medications and procedures) such as nutritional supplements, pain medications, antibiotics, antifungals, iron supplements, antiemetics/antinauseants, antidiarrheals, antivirals, radiation therapy, bone-targeting agents (eg, bisphosphonates, denosumab), erythropoiesis-stimulating agents, granulocyte-colony stimulating factors, folic acid, red blood cell transfusion, and platelet transfusion during the first line of treatment with sunitinib.

8.3.4. Treatment-related Outcomes

Treatment-related AEs (eg, hypertension, neutropenia, thrombocytopenia, fatigue, stomatitis) will be documented for the duration of first-line treatment with sunitinib. Frequency of toxicity evaluation (eg, every 6 weeks) and the method of evaluation (eg, radiological evaluations by computed tomography, magnetic resonance imaging with measurable lesions via Response Evaluation Criteria in Solid Tumors [RECIST]) will also be documented.

Dates of progression and death (ie, whether the patient died during the follow-up period and whether the death was related to RCC) will be documented. Disease progression and survival estimates will be derived from these measures and calculated from the date of diagnosis of metastatic RCC, the start of first-line treatment line with 4/2 or 2/1 sunitinib, and the time of switch to the 2/1 schedule (among those who initiated on the 4/2 schedule). Survival estimates will include, but are not limited to, the following:

- Overall survival;
- PFS;
- Time to second-line initiation.

8.4. Data Sources and Data Collection Method

Data will be abstracted from the medical records of patients at various treatment centers in the selected countries. 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, and health outcomes that may otherwise be unavailable in a standardized manner. The use of medical record abstraction allows for the development of a highly customized CRF that meets the specific needs of this study.

While ethics activities at sites are ongoing, the CRF will be programmed into a web-based eCRF. Following ethics approval and finalization of the eCRF, PPD will send secure links of the eCRF to the PI or the designated study coordinator of each site. The PI and/or their designated research team will screen their patients' records to identify eligible patient records. Once a potential medical record is identified, the PI and/or their research team will answer multiple screening questions in the eCRF to confirm the selected medical record is eligible for inclusion. After the medical record is determined to be eligible, the PI and/or their research team will complete the eCRF form by retrospectively reviewing all available data in the medical record. See Section 8.9 for a detailed review of the limitations of this study type. It is anticipated that it will take an abstractor approximately 30 to 45 minutes to complete the CRF for each patient record.

8.5. Study Size

A convenience sample of at least 150 medical record abstractions will be targeted across all sites and 7 Latin American countries. As this study is descriptive in nature, no formal power calculations were conducted to determine the sample size for this study. This study does not involve hypothesis testing (via statistical testing) and is primarily being conducted to understand clinical characteristics, sunitinib treatment patterns, and health outcomes.

It is anticipated that all participating sites will provide data for all eligible patients. If any site estimates a greater number of eligible patients than needed to meet the total study sample size in the respective country, that site will be required to select a quasi-random sample of eligible patients for the study. This process will entail selection of medical records for patients whose last names begin with a randomly generated letter between A and Z, provided to the abstractor during data collection. For example, if "M" is the randomly generated first letter and if the abstractor does not have any patients who meet the study criteria and whose last name begins with "M," then they will select a patient whose last name begins with the next letter in alphabetical order (in this example, "N"). Due to variations in the distribution of first letters among last names, patients may not have an equal probability of inclusion in the study.

The PIs will be responsible for meeting sample size expectations at their respective sites. In the event that sample sizes are not met with the selected sites, other sites with additional eligible patients may be asked to provide data for additional patients or new sites may be recruited. The anticipated sample size in each country will be fixed; however, the sample obtained from each participating site will vary, depending on the available sample.

8.6. Data Management

PPD will perform the analyses described in this proposal using Statistical Analysis Software (SAS) application housed on PPD secure, large-capacity, high-performance Linux mainframe. Experienced PPD 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, PPD implements several practice standards for statistical programming, database management, and documentation for all projects involving databases analyses. The following 3 steps will be undertaken to achieve this high level of quality:

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

8.6.1. 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.

8.6.2. 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.

8.6.3. 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.

8.6.4. 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. When appropriate, we also will have a separate analyst review these listings independent of the programmer.

8.6.5. 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.

8.6.6. Validation Documentation

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

8.6.7. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF 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 CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

To comply with privacy requirements, physicians (or the designated research team) will be abstracting the clinical and safety data directly from patients' medical records to the eCRF, and neither Pfizer nor PPD will have access to patients' medical records. To decrease chances of data-entry errors and resulting inaccuracies, data checks will be programmed into the eCRF, where possible, to improve the internal consistency of the data. Physicians (or the designated research team) will be able to make changes to the data in the eCRF before it is submitted, and any requests for corrections to entries made in the eCRFs will be dated and explained (if necessary).

8.6.8. Database Storage and 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, CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, 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 clinical 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 15 years after completion or discontinuation of the study, unless specific Pfizer protocols or PPD policies explicitly prohibit this. If any data-cleaning activities or other analyses need to be repeated for any reason, this retention procedure will allow quick and efficient access to the data sets. If requested by Pfizer, the raw analytical files will be provided to Pfizer.

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

8.7. Data Analysis

All measures described in Section 8.3 will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations of continuous variables of interest and frequency distributions for categorical variables. Time-to-event outcomes (ie, overall survival, PFS, time to second-line initiation) will be described using the Kaplan-Meier method. All analyses will be conducted using SAS (version 9.4 or later) statistical software. Samples of patients who switched from the 4/2 to the 2/1 schedule from each country will be pooled and analyzed in aggregate. The sample of patients from Brazil who initiated first-line sunitinib on the 2/1 schedule will be analyzed separately. Results may be described for up to 2 subgroups that will be determined after the initial review of the data (eg, number of cycle on the 4/2 schedule).

As this study is descriptive and designed to generate hypotheses, direct comparisons between outcomes on the 4/2 schedule and on the 2/1 schedule will not be conducted. Potential confounders, such as characteristics that prompt the switch and other possible time-dependent factors (eg, dose modifications and delays), are not comprehensively collected or controlled for in this study design. Variability in timing of the switch from a 4/2 to a 2/1 schedule will affect the distribution of time-dependent outcomes after the switch (even in the absence of immortal-time bias), as some patients may switch “early” in their first-line therapy and others may switch “later.” Thus, causal inferences about the benefit of switching treatment schedules cannot be drawn.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan, which will be dated, filed and maintained by the sponsor. The statistical analysis plan may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality Control

The following data checks will be performed for all data collected in the eCRF:

- Check for illogical or unusual data (eg, treatment starting prior to diagnosis);
- Check for speeders (ie, abstractors who seem to skim through the eCRF by falling below a certain tolerance time interval of an estimated average duration needed for completing the form);
- Check for responders with a typical unrealistic response pattern, such as always checking the same value in a numerical scale or responding in an erratic, implausible manner to certain questions;
- Check for an extremely high percentage of "Do not know" or "Data not available" responses;
- Check for an extremely high percentage of answering filter questions in a way so as to avoid having to answer subsequent questions in more detail.

The PPD Office of Quality Assurance (OQA) is an independent unit that reports to the Vice President of PPD 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.

PPD 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 for involved subcontractors, 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.

8.9. Limitations

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

- Patients selected for study inclusion represent a "convenience" sample, in that the records will be obtained from sites who are willing to participate in the study. Therefore, study findings may not be generalizable to the overall population of patients with metastatic RCC or sites where RCC is treated in the selected countries.

- All data captured in the eCRF will be limited to information available in the patients' medical records held by the sites participating in the study. Information on health care services received outside the sites' care setting that is not recorded in the medical record will be unavailable for this study (eg, treatment for AEs received through a separate hospital).

- To increase the chance of random selection of eligible medical records at sites that estimate a larger than needed eligible population, abstractors will be asked to select medical records for patients whose last names begin with a randomly generated letter between A and Z. Due to variations in the distribution of first letters among last names, patients may not have an equal probability of inclusion in the study.

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

- This study is designed to describe characteristics and outcomes of patients who switched from the 4/2 to the 2/1 sunitinib schedule. Potential confounders, such as characteristics that prompt the switch and other possible time-dependent factors (eg, dose modifications and delays), are not comprehensively collected or controlled in this study design. Variability in timing of the switch from a 4/2 to a 2/1 schedule will affect the distribution of time-dependent outcomes after the switch (even in the absence of immortal-time bias), as some patients may switch "early" in their first-line therapy and others may switch "later." Thus, causal inferences about the benefit of switching treatment schedules cannot be drawn.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

The PIs at each site will be provided with a summary of the protocol, objectives, and methods as well as their rights and responsibilities prior to providing their consent to participate in the study. Physician or participating site staff's consent will be obtained electronically prior to participating in the medical record abstraction.

Patient medical record data may contain highly sensitive and private personal health information. Therefore, the following data collection strategies will be implemented to ensure the data collected in this study strictly comply with definitions of deidentified or anonymous data:

- At any point in this study, members of the PI's direct health care team or designated research team are the only individuals with access to the patient's medical record data containing potentially identifiable information. The study team (ie, PPD and Pfizer) will not view, obtain, or have access to any identifiable health information such as patient name, address, date of birth, or other personal identifiers.

- Patient identifiers such as name, address, telephone number, e-mail address, health record/beneficiary number, biometric data, and photographs are not relevant to this study and will not be collected or viewed at any point by the study team.

As the data used in this study are anonymous, this study poses minimal risk to patients whose medical record data are analyzed. With anonymous data, 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 in a region (including those outside the physicians/sites participating in the study) 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.

The PI's in this study will be subject to different, albeit remote, risks compared with patients. It is conceivable that participation in the study may divert a small amount of the physicians' time and resources away from clinical activities to allow for their participation in this research. However, it is expected that these physicians will adequately manage their time.

Only the abstractors who directly enter the patient data into the secure eCRF will see explicit patient identifying information. The web portal used for data collection is hosted in a secure data center. This data center offers a secure environment that minimizes the chance of a security breach, thereby allowing access only to authorized persons with valid usernames and passwords. Only anonymized data will be held at the data center. 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.

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 when required by applicable laws.

9.2. 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. If ethics requirements at a participating site or in a given country require informed consent, a waiver of informed consent will be sought.

9.3. Participation Withdrawal

Participating sites may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a site withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.4. 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.

9.5. 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 will follow generally accepted research practices described in the following:

- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) https://www.pharmacoepi.org/resources/guidelines_08027.cfm.

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp.

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/.

Ethics review requirements and processes for retrospective studies vary between countries and are governed by local standards. This study will be conducted in accordance with such standards in each country.

PPD will work in collaboration with the site PIs to submit the necessary ethics review applications in each country at both the site and national levels, where applicable. However, the site PIs will be responsible for submissions to the ethics review board (ERB), completion of notifications/submissions, and follow-up with ERBs to obtain final approvals where appropriate. The following activities are anticipated:

- Argentina:
  - No national-level approval by the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) required;
  - The site must be registered or accredited within the Jurisdiction of the Ministry of Justice;
  - ERB review is required at each of the participating sites.
- Brazil:
  - No national-level approval by the Agência Nacional de Vigilância Sanitária (ANVISA) required;
  - Comissão Nacional de Ética em Pesquisa (CONEP) approval is required for at least one site, which will serve as the lead site; this serves as a national ethics approval;
  - ERB review is required at each of the participating sites.
- Ecuador:
  - Approval is required by an Ethics Committee of Human Research (CEISH) recognized by the Ministry of Public Health;
  - ERB review is required at of the participating sites.

- Colombia:
    - Notification to the Instituto Nacional de Vigilância de Medicamentos y Alimentos (INVIMA) is required;
    - ERB review is required at each of the participating sites.
- Costa Rica:
    - National-level approval by the Consejo Nacional de Investigación en Salud (CONIS) required;
    - Approval is required by the Centro de Desarrollo Estratégico e Información en Salud y Seguridad Social (CENDEISSS);
    - ERB review is required at the participating sites.
- Peru:
    - No national-level approval by the Instituto Nacional de Salud (INS) required;
    - Ethics Committee approval is required for each site (Ethics Committee must be registered with the INS competent authority).
- Mexico:
    - Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) approval is required;
    - Ethics Committee approval is required for each site (the Ethics Committee must be approved by the La Comisión Nacional de Bioética (COMBIOETICA) and COFEPRIS and approval must be current until the study ends.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. 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 healthcare 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 data collection tool 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, gender, 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.

11. 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 which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. REFERENCES

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13. LIST OF TABLES

None.

14. LIST OF FIGURES