Monitoring of Treatment Related Toxicities from Oral Targeted Agents and Immunotherapy Among Patients with Advanced Renal Cell Carcinoma (RCC) Using Carevive Software, a Single-Arm Phase II Feasibility Study.

Study Protocol

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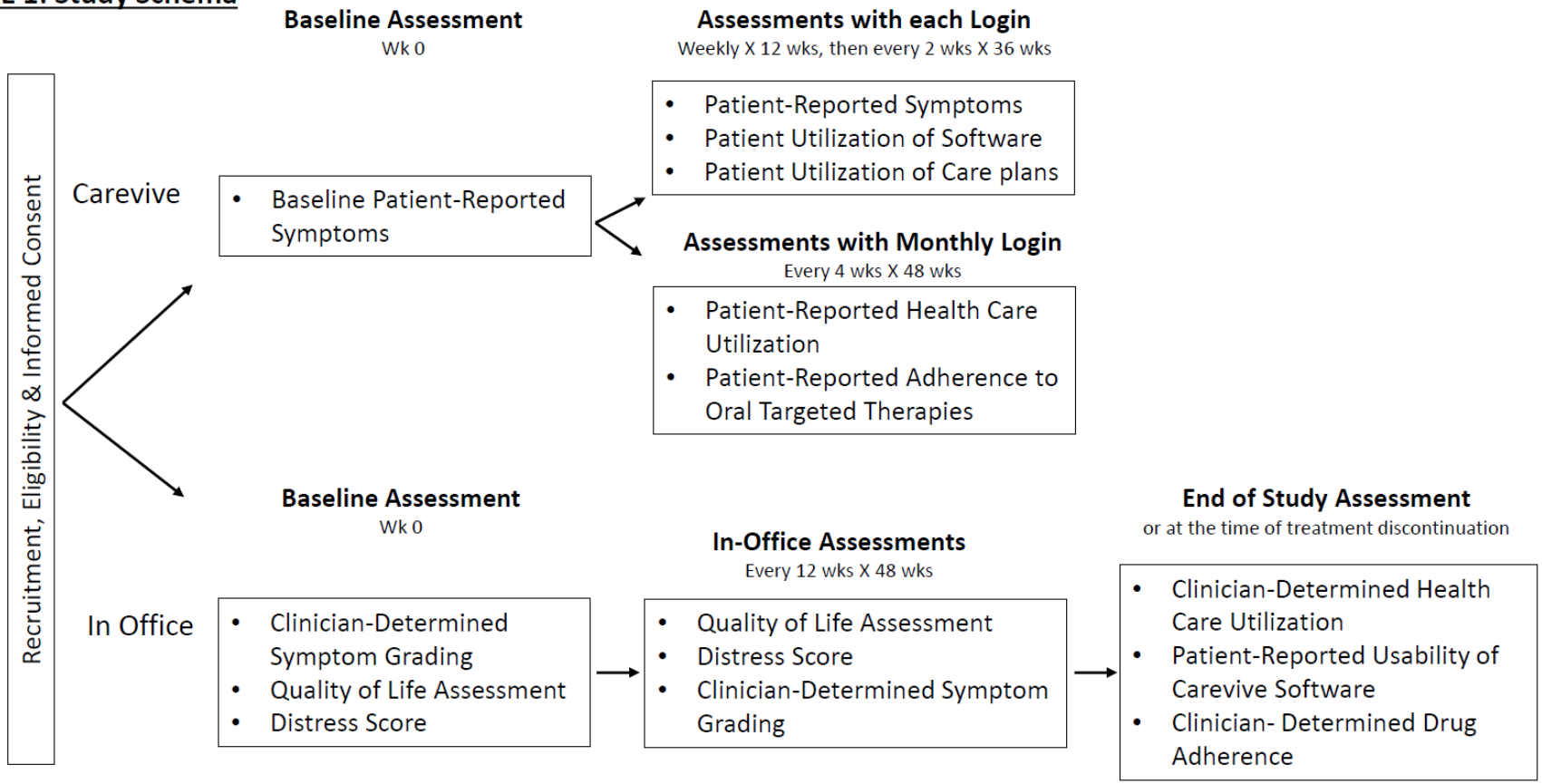
FIGURE 1: Study Schema



1.0 STUDY OVERVIEW, PURPOSE, AND BACKGROUND

1.1 Overview

Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for >90% of all kidney neoplasms. There will be an estimated 62,700 new diagnoses of RCC in the United States this year, as well as 14,240 deaths from this disease [1, 2]. Early stage RCCs are typically treated with surgery alone, but once distant metastases have developed, RCC is rarely curable. The typical treatment course of metastatic RCC involves cytoreductive nephrectomy followed by systemic therapy [3]. Traditional intravenous chemotherapies are not utilized due to dismal response rates [4]. For decades, the only available agents for metastatic RCC were cytokine infusions which can be difficult for patients to tolerate and sometimes require hospital admissions for administration and monitoring. In 2005, the RCC treatment paradigm began to change rapidly with the approval of tyrosine kinase inhibitors sorafenib and sunitinib. Since that time, eight other targeted therapies have also been approved for the treatment of metastatic RCC. At present, the most commonly prescribed first-line agents are oral targeted therapies[5], a group of inhibitors which are designed to target vascular endothelial growth factor (VEGF), other tyrosine kinases and mechanistic target of rapamycin (mTOR). While median overall survival data for metastatic RCC is difficult to accurately assess due to the advancement of therapy in recent years, there is a trend towards longer survival times in clinical trials. In fact, when pazopanib was studied as a first-line agent, the median OS of these patients with metastatic RCC was >2.5 years [6, 7]. There are currently seven approved oral targeted therapies for RCC, these are axitinib, cabozantinib, sunitinib, lenvatinib, sorafenib, pazopanib and everolimus; the first six agents are all tyrosine kinase inhibitors (TKIs) while everolimus is an mTOR inhibitor [2]. Immunotherapy with the PD-1 checkpoint inhibitor nivolumab was approved in 2015 and is also being used with increasing frequency for the treatment of metastatic RCC [3]. Immunotherapy and oral targeted therapy offer superior convenience to patients over RCC treatments of past decades. Patients are now able to spend more time at home and less in the health care setting. While this is clearly preferable for patients, they now have less opportunity for face-to-face interaction with their health care providers to report the side effects of their cancer treatment.

With computers and smart devices now being pervasive in American homes [8], there is a unique opportunity to exploit technology for patient side effect reporting and management. Additionally, there has been much more emphasis on patient-reported outcomes in recent years for both improved patient care and the monitoring of clinical trial outcomes [9, 10]. Electronic cancer symptom self-reporting has already been determined to be feasible and effective in cancer patients [9]. The primary goal of this project is to <u>determine if electronic side effect monitoring, combined with software generated self-care plans, is feasible to implement in patients with metastatic RCC who are being treated with immunotherapy or oral targeted therapy.</u> We have therefore, partnered with Carevive Systems, a software company that is committed to improving the well-being of cancer patients through the generation of personalized self-care plans.

1.2 Carevive Software

Carevive Systems, Inc. is a health information technology company whose mission is to improve clinical and quality of life outcomes for cancer patients. They build clinical practice and patient engagement tools used across the cancer continuum to help cancer centers meet quality standards tied to reimbursement and accreditation. For more about Carevive Clinical Systems, see www.carevive.com.

In this study, Carevive will deliver a link to subjects so that an online survey can be completed. The survey will occur weekly for the first 12 weeks of the study and will be spaced out to every other week thereafter. The questions will mostly focus on side effects from their cancer therapy, as well as a few questions about drug compliance and healthcare utilization. After completion of the survey, the subjects will be given a care plan with at home self-management options for drug-related toxicities.

1.3 Targeted Therapies for the Treatment of Metastatic RCC.

For decades the only effective systemic therapies available for metastatic RCC were the cytokines interferon-alpha and interleukin-2 (IL-2), and once patients failed/progressed with cytokine therapy, there were no second-line agents available to them. The treatment paradigm for metastatic RCC began to shift in 2005-2006, with the Food and Drug Administration (FDA) approval of two oral tyrosine kinase inhibitors (TKIs), sunitib and sorafenib. TKIs work by impeding cell signaling pathways which are essential to tumor proliferation, survival and angiogenesis. Sunitinib and sorafenib were shown to enhance progression free survival (PFS) by approximately 3 and 6 months respectively, [11, 12] in metastatic RCC patients. These agents are both multikinase inhibitors that act on intracellular Raf kinases, as well as several cell surface kinases. The potential side effect profiles of these agents are broad, but most commonly include fatigue, diarrhea, nausea, hand-foot syndrome, abdominal pain and mouth sores/pain. Pazopanib, another multi-kinase TKI, was FDA approved in 2009 based on an enhanced PFS compared to placebo and subsequent studies showed non-inferiority to sunitinib [13]. Pazopanib has a similar side effect profile to the earlier TKIs, including diarrhea, nausea, decreased appetite, weight loss, fatigue, skin rash, shortness of breath, cough, and hair discoloration. In 2012, axitinib was approved for second-line used based on a 1.4 month enhanced PFS [14]. It is unique in that it selectively targets just one family of kinases; common side effects include fatigue, hand-foot syndrome, diarrhea, anorexia, nausea, vomiting, constipation and cough/dyspnea. Later in 2012, everolimus was also approved for second-line RCC therapy, with an enhanced PFS of 3 months in that setting [15]. Everolimus is an mTOR inhibitor and common side effects include fatigue, mouth sores, diarrhea, nausea, skin rash and cough. The two most recently approved oral targeted therapies, cabozantinib and lenvatinib, are both multitargeted TKIs. While cabozantinib was studied as a single-agent, lenvatinib was used in combination with everolimus [16, 17]. Common side effects of these drugs include fatigue, headache, hand-foot syndrome, diarrhea, anorexia, edema, hair discoloration nausea, mouth sores, vomiting, abdominal pain, arthralgia, constipation and cough.

Immunotherapy is a new form of cancer treatment that has been found to be effective in a variety of cancer types over the last several years. In metastatic RCC, nivolumab, which is a monoclonal PD-

1 blocking antibody, was also approved in 2015 for second-line treatment based on an enhanced patient overall survival by 6 months [18]. Nivolumab works by blocking the interaction of PD-L1 on tumor cells and the PD-1 receptor on T cell surfaces, thereby activating the immune system against cancer cells. Nivolumab is delivered as an intravenous infusion every two weeks and is being prescribed with increasing frequency. Therefore, although it is not an orally available agent, it is prudent to include nivolumab in our study of side effect reporting and management since many metastatic RCC patients will receive this therapy at some point during the course of their treatment. The most common side effects experienced with nivolumab are fatigue, rash, diarrhea, anorexia, nausea, constipation, vomiting, cough and shortness of breath.

Given the overall side effects profiles of the TKIs, everolimus and nivolumab, we have chosen the following eleven common side effects for patient electronic reporting and self-management in this study: diarrhea, nausea, vomiting, fatigue, hand/foot syndrome, rash, abdominal pain, anorexia, mouth sores, cough and shortness of breath.

1.4 Evidence for Integration of Technology into Symptom Management in Cancer

To improve communication between patients and their cancer care providers, electronic self-reporting of symptoms had been studied and found to be effective [19, 20]. One such reporting system, ESRA-C has been shown to reduce symptom distress during cancer therapy and their updated version, the ESRA-C-II resulted in enhanced patient verbal reporting of symptom and quality of life issues [9, 21]. Our study would differ from ESRA-C in that we are looking at one specific cancer type (metastatic RCC) and we are specifically addressing symptoms related to the cancer therapy. Also our format would be delivered to the patient in their home, where they could complete it at their convenience, whereas the ESRA-C was delivered in the office waiting room prior to appointments.

1.5 PRO-CTCAE

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) is a tool designed to standardize the reporting of clinician reported adverse events (AE) during clinical trial. This exhaustive list of symptoms, physical findings, and lab abnormalities are graded using a severity scale [10]. Approximately 10% of the adverse events in the CTCAE are patient symptoms, which are conveyed from the patient to the clinician and then recorded. This second-hand method of AE reporting has been shown to be unreliable [22], with a physician tendency to under-rate patient symptoms [23]. To improve adverse event reporting, the National Cancer Institute (NCI) developed a patient-reported outcome supplement to the CTCAE, called PRO-CTCAE. PRO-CTCAE includes questions on 124 potential patient reported items. The patient directly completes the questions through either a computer interface or an automated telephone system, eliminating the need for information to pass through a clinician. Once further validation of this reliable questionnaire is done, it is intended to be used to monitor adverse events in clinical trials [10]. We will be using the format of PRO-CTCAE in our side effect surveys since it is an independently verified strategy for side effect monitoring. We will focus on the eleven common side effects listed in the previous section to prevent the surveys from being overly burdensome to our patients.

1.6 Significance and Innovation of Study

Clinician-initiated grading of treatment side effects in cancer has previously been shown to be unreliable [23]. Our intention is to implement a software program to more accurately obtain patient side effect information and to provide patients with corresponding self-care plans. Oral targeted RCC therapies and immunotherapy carry significant side effects. The goal of this project is to generate and implement self-care plans that we believe will empower our patients to perform self-care in order to minimize treatment-related side effects between visits. These care plans will include basic side effect home management but will automatically trigger our staff pharmacists with severe side effects that need immediate personal assistance. To our knowledge, this is the first study seeking to validate an RCC-treatment specific, electronic side effect reporting tool. This strategy of AE monitoring and management via an automated self-care plan has the potential to enhance self-reporting, decrease unnecessary clinic visits and telephone calls and provide overall better patient care. Additionally, to our knowledge this is the first electronic reporting system that is collecting side effect data in the PRO-CTCAE format. Utilizing the PRO-CTCAE questions will enable this software to be more readily incorporated as a reporting tool in future clinical trials

2.0. HYPOTHESES AND AIMS

2.1. Overall Hypothesis

We hypothesize that Carevive software, which monitors treatment-related toxicities and then generates self-care management plans for these symptoms, will be feasible to implement among patients with metastatic renal cell carcinoma (RCC). Additionally we intend to collect preliminary data on treatment-related toxicities, quality of life, distress level, and drug adherence.

2.2. Primary Aim

2.2.1. Assess the feasibility of Carevive software implementation for at-home monitoring and management of treatment-related toxicities from oral targeted agents/immunotherapy among patients with metastatic RCC.

- To determine the demand for this intervention by examining the number and percentage of subjects with RCC who 1) use Carevive software to report their treatment-related symptoms; and 2) utilize the Carevive software generated care plan for management of their treatment-related toxicities.
- To determine the practicality of the intervention, by analyzing the reasons why subjects fail to self-report treatment-related toxicities or utilize software generated care plans after enrollment.
- To assess the acceptability of this intervention with validated patient reported usability scores of the software.
- To determine potential implementation obstacles of the intervention, by assessing the reasons eligible study candidates decline participation.

2.3. Secondary Aim

2.3.1. Collect preliminary data on RCC patients' symptoms, health care utilization, quality of life, distress level and oral drug adherence while on targeted therapy or immunotherapy.

- To determine how patients' treatment-related toxicities correlate to their quality of life, distress level, drug adherence and health care utilization.

3.0. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1 Number of Subjects: We expect to recruit 50 advanced renal cell carcinoma patients from the genitourinary oncology program at Wilmot Cancer Institute of the University of Rochester Medical Center over a one-year period.

3.2 Gender of Subjects: Both men and women will be enrolled in this study. Advanced RCC is known to be almost twice as prevalent in men than women [24], therefore we can expect a roughly 2:1 male to female enrollment rate.

3.3 Age of Subjects: We will recruit patients 18 years and older for this study, however RCC is very uncommon in patients <45 years of age and typically affects adults between the ages of 45 and 84 [1].

3.4 Racial and Ethnic Origin: This study has no enrollment restrictions based upon race or ethnic origin. RCC is known to be less prevalent in Asian and Pacific Islanders [1].

3.5 Inclusion Criteria:

- 3.5.1 Diagnosis of histologically confirmed renal cell carcinoma of any subtype with either pathological or radiographic evidence of metastatic disease
- 3.5.2 Greater than 18 years of age
- **3.5.3** A participating Wilmot Cancer Center oncologist has determined that candidate should be started on either oral targeted therapy or immunotherapy for treatment of their advanced RCC; t**his can be for first-line or any subsequent line therapy**
- 3.5.4 Able to provide written informed consent
- 3.5.5 Proficient in the English language and self-reports as literate
- 3.5.6 Must have an active email address or access to a smart device

3.6 Exclusion Criteria:

- 3.6.1 Women cannot be breast-feeding
- 3.6.2 Does not have regular access to the internet
- 3.6.3 Unable to come to the Wilmot Cancer Center for appointments every 3-4 months for routine visits with their primary oncologist
- 3.6.4 Subjects who were on the study previously will not be allowed to re-enroll in the event of a treatment change

3.7 Vulnerable Subjects: No special classes of subjects such as fetuses, neonates, children, pregnant women, prisoners, institutionalized individuals or other vulnerable populations will be recruited.

4.0. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

4.1 Identification and Recruitment

The study coordinator and investigators will review active patient records to identify all patients who meet eligibility criteria. Potential subjects will be approached for interest at their next scheduled visit with their genitourinary oncologist at the Wilmot Cancer Center. After identification of potential subjects for the study, Drs. Chunkit Fung (PI), Deepak Sahasrabudhe and Adrienne Victor, who are medical oncologists at the Wilmot Cancer Institute, will introduce the study to potentially eligible subjects.

4.2 Consent Process

For eligible subjects who are interested in study participation, a study team member will walk the subject through the consent form to ensure comprehension and the subject will be given the option to sign the consent form. The study team member will be available to answer any questions that the subjects may have about the study prior to consenting and throughout the entire study period. If the subject opts not to participate in the study, we will record their reason in a screening log which will not be connected to any identifying patient information.

5.0. REGISTRATION

5.1 Registration Procedures

To enroll a subject who meets the eligibility criteria (see sections 3.5 and 3.6) and who has signed the informed consent documents, log on to the *Research Electronic Data Capture (REDCap)* and enter the subject information as outlined below:

- A subject ID number will be assigned in sequential order as the subjects are enrolled into the study. The 2-digit number will be used to identify the subject on all study forms.
- First and last initials
- Birth date (MM/DD/YYYY)
- Gender
- Race
- Nine-digit zip code

6.0. METHODS AND STUDY PROCEDURES

6.1 Overview of Study:

We will conduct a phase II, single-arm clinical trial to assess the feasibility of reporting and managing side effects from oral targeted therapy or immunotherapy, through Carevive software, in patients who have advanced RCC. The study will begin when the consented subject starts a new therapy, either an oral targeted agent (pazopanib, sunitinib, axitinib, cabozantinib, lenvitinib, everolimus) or infusional immunotherapy (nivolumab), and will continue for a duration of 48 weeks or until drug is permanently discontinued by their primary oncologist. All study subjects will be asked to log their symptoms through Carevive software weekly for 12 weeks and then every other week for the next 36 weeks. Based on their symptoms, subjects will receive self-management instructions through the software (if applicable). Subjects will also be asked to monitor their medication compliance and health care utilization through the Carevive software once every four weeks for the length of the study. In addition, subjects will be asked to fill out a survey at their medical oncology office visits approximately every 3 months. This survey will include a distress assessment and a quality of life questionnaire. During these visits, a clinician will formally assess the subject's medication related adverse events. At the end of the study, the subject will be asked to fill out an in-office survey rating the usability of the Carevive software. On study completion, the subject's electronic medical record will be reviewed to determine health care utilization and oral targeted therapy refill history during the study period.

6.2 Screening and Recruitment

The study coordinator and investigators will review records to identify all active patients who meet eligibility criteria. Potential subjects will be approached for interest in participation at their next scheduled visit through the Genitourinary Medical Oncology Program at the Wilmot Cancer Center. After identification of potential subjects for the study, Drs. Chunkit Fung, Deepak Sahasrabudhe and Adrienne Victor, who are medical oncologist at the Wilmot Cancer Institute Genitourinary Oncology Program, will introduce the study to potential subjects.

6.3 Consent Process

For eligible subjects who are interested in study participation, the study coordinator or study staff member will come to the Wilmot Cancer Institute Genitourinary Oncology Clinic to review the informed consent process. The study coordinator or study staff member will walk the subjects through the consent form to ensure comprehension and the subjects will be given the option to sign the consent form. The study coordinator or study staff member will be available to answer any questions the subjects may have about any aspect of the study prior to consenting throughout the entire study period.

Subjects may choose to sign the informed consent immediately in the clinic or at a subsequent visit with the study coordinator or study staff after reviewing the informed consent at home and discussing it with others. Subjects must sign the consent and complete a baseline assessment prior to starting their new treatment with either oral targeted therapy or immunotherapy in order to remain eligible. The study coordinator is primarily responsible for obtaining all of the informed consents from study subjects; however the study staff PI, Dr. Fung and other co-investigators may obtain consents in cases where the study coordinator is not available. After completion of the consent process, the study team member will help the subject to schedule a baseline assessment which must occur within the two weeks prior to starting the new therapy.

If the subject does not wish to consent to the study, their reason for declining participation will be recorded in a deidentified manner via a screening log.

6.4 Baseline Assessment (Week 0)

The baseline assessment can occur on the day of consent if the subject is going to be started on treatment with either a new oral targeted agent or a new immunotherapy within the following two weeks. At this visit, the physician will perform a baseline toxicity check following the Common Terminology Criteria for Adverse Events (CTCAE) which will be documented in the subject's electronic medical record. Specifically, the following CTCAE parameters will be assessed: diarrhea, nausea, vomiting, fatigue, abdominal pain, rash, anorexia, weight loss, oral mucositis, cough and shortness of breath. The subject will be asked to fill out a demographics form, kidney cancer specific quality of life survey called the FKSI-DRS (Functional Assessment of Cancer Therapy-Kidney – Disease Related Symptoms) and to rank their distress using the NCCN (National Cancer Consortium Network) Distress Thermometer and Problem List for Patients on a tablet while in office. The subject will then log into the Carevive system on an office computer or tablet, provide their email address and complete an initial survey, which will assess their baseline symptoms using Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) questions for the following categories: diarrhea, nausea, vomiting, fatigue, hand/foot syndrome, rash, abdominal pain, anorexia, mouth sores, cough and shortness of breath.

6.5 Study Intervention - Carevive Assessments and Care plans (Week 1-12 and 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48)

The initial survey will occur in office at the week 0 time point. Carevive will then email the subject a link to the survey weekly for the first 12 weeks and then every other week for 36 weeks, to complete 48 weeks or until the subject comes off of the study. This survey will consist of PRO-CTCAE adverse event questions. Subjects will then be provided with self-care management through this automated system. Self-care plans provide advice on managing the symptoms one is experiencing. For example, if the questionnaire indicates a subject is having "occasional" diarrhea, they will be instructed to try an over the counter anti-diarrheal, loperamide, and to keep a stool diary to identify any triggers. They will also be instructed to call the office if their bowel movements increase to 4 or more per day. If the diarrhea is instead rated as "frequently" or "almost constant" the subject will again be instructed to try loperamide but they will also be told to call their cancer care provider immediately, while also stressing the importance of hydration (drinking 8-10 glasses of water daily), and modifying the diet to avoid caffeine, alcohol, spicy foods and dairy.

Every four weeks the survey will also include questions about healthcare utilization and drug adherence. If a subject misses a login they will be sent a reminder the following week, if they miss two logins Carevive will notify our staff who will follow-up with them via telephone.

6.6 In-Office Assessments (Week 12, 24, 36 and 48)

Every 3-4 months at routine visits, the physician will perform a toxicity check and will document the grade of the following CTCAE parameters in the subject's electronic medical record: diarrhea, nausea, vomiting, fatigue, abdominal pain, rash, anorexia, weight loss, oral mucositis, cough and shortness of breath. The subject will again be asked to fill out a FKSI-DRS quality of life survey and the "NCCN Distress Thermometer and Problem List for Patients" on a tablet or computer while they are in the office.

6.7 Final Assessment

At the 48 week timepoint, or when the subject withdraws from study, we will ask them to fill out the previously well-validated System Usability Scale (SUS) questionnaire on a tablet rating their experience with the Carevive software and care plans.

7.0. SUBJECT CONSENT AND WITHDRAWAL

7.1 Informed Consent

Current state, federal and institutional regulations concerning informed consent will be followed. Participation in this study is voluntary. Subjects are free not to take part or to withdraw at any time, for whatever reason, without risking loss of present or future care they would otherwise expect to receive. In the event that a subject does withdraw from the study, the information they have already provided will be kept in a confidential manner. Subjects may discontinue participation in the study at any time if they decide they do not wish to take part any longer.

7.2 Withdrawal

Subjects may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate (for example, in the event that treatment needs to be changed).

The investigators may withdraw the subject from the study in the event of concurrent severe illness, adverse events, other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation, non-compliance, or other administrative reasons.

Reasons for withdrawal of the subject prior to completion of the study must be stated in a Case Report Form (CRF) and in the site source documentation for all study subjects who were enrolled.

8.0. DATA AND SAFETY MONITORING

This study is considered to be of minimal risk and low complexity and will follow the Data Safety Monitoring Plan outlined below:

1. Study investigators will conduct continuous review of patient accrual, eligibility, data collection, and patient safety;
2. There are no or minimal side effects expected related to the study intervention(s);
3. The Data Safety Monitoring Committee will monitor the study on an annual basis through review of RSRB reports;
4. This study may be selected for audit as part of the DSMC data monitoring activities.
5. In the event of an unexpected AND possibly related toxicity the Study Investigator is responsible for notifying the Safety Office of DSMC Chair within 10 calendar days.

9.0. RISK/BENEFIT ASSESSMENT

9.1. Benefits to Subjects

It is expected that participation in this study will involve minimal risk to the participant. Potential benefits from participation include improved symptom assessment and management of drug-induced side effects. Knowledge gained from this study may help improve these activities for cancer patients in the future. As such, it is expected that the benefits of this study outweigh the potential risks. There are no monetary or other secondary benefits.

9.2 Risks to Subjects

This survey study is expected to pose minimal risk to participants. Potential risks include a breach of confidentiality and respondent burden, particularly for cancer patient participants. It is expected that a patient's level of burden will vary based on their overall condition, family and social support and participation in other research studies. Risks of using electronic devices to answer surveys include use of data if not connected to wireless free internet and loss of confidentiality if devices or computers are shared.

9.3 Adequacy of Protection against Risk

To minimize respondent burden, we will inform all participants that participation in the proposed study is voluntary and they may discontinue participation at any time. This study involves obtaining access to subject's medical records and steps must be taken to protect both participant data and identity. The following confidentiality protection steps will be taken: 1) Research staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure understanding of the ethical issues involved in this research. 2) Only the research staff will know the name, identification number, and contact information of participants. The list that links the participant's name with ID number will be kept on an encrypted drive accessible only by the research staff. 3) Consent forms will be kept in locked filing cabinets on the second floor of the Wilmot Cancer Center, in a restricted area with swipe access and will be accessible only by research

staff, and 4) any personal identifiers linked to data will be removed and replaced by non-identifying ID numbers in all records. The electronic files that contain quantitative data will be stored on secure University of Rochester Medical Center file server. These files will be password protected and accessible only by the WCC study team.

In addition, the Carevive electronic platform complies completely with HIPAA standards. Security and confidentiality of the data is ensured through a variety of steps: 1) secured/encrypted SSL/TLS connections, 2) user accounts with unique usernames and passwords, 3) HIPAA compliant cloud hosting for all data stored within the Carevive platform through Firehost, Inc., a company that specializes in secure cloud hosting (http://www.firehost.com/secure-cloud/compliant/hipaa). To mitigate risk associated with using electronic devices, we recommend that all devices are password protected and that the subjects log off of their web browser and/or email application prior to leaving their device unattended. We also advise the avoidance of the employer's computer to access the surveys.

10.0 Costs to the Subject

The subject will not incur any direct costs as a result of participation in the study. As stated above, all subjects will be on standard of care therapies, which will be prescribed by their oncology team. The subject's insurance and/or the subject will be billed for their standard of care treatment just as they would if they were not participating in this study. Scheduled in-office assessments and surveys will be done at routine clinic visits and will not result in any additional charges.

1.0 Payment for Participation

There will be no reimbursements or payments of any kind for participation in this study.

12.0 A COLLECTION AND MEASURES

12.1 Primary Study Outcome Measures: The primary outcome will be the feasibility of implementing at home side effect self-assessment and monitoring software.

12.1.1 Carevive Survey Usage Rates

Carevive software will track subject compliance with survey login and whether they access the generated care plans. The clinical team will be notified if a subject misses a login after failing to respond to a reminder notification.

12.1.2 Reasons Participants Do Not Complete Survey or Utilize Care Plans

At the following login, subject will be asked the reason they did not login in the previous time point/time points (if applicable) and why they did not access the care plan.

12.1.3 Software Usability Scoring:

At the 48 week time point or at the point of subject withdrawal from study, they will be asked to take the System Usability Scale [25]. This is a 10 question survey where responses range from "Strongly Disagree" to "Strongly Agree," which are ranked with corresponding numbers. The survey provides us with a score of between 0 and 40 which is then multiplied by 2.5 to convert to a scale of 0 to 100. A SUS score above a 68 would be considered above average and anything below 68 is below average [25].

12.1.4 Reasons for Declining Study Participation

If a subject declines to participation in the study, he/she will be asked to provide a reason for declination which will be recorded in a screening log.

12.2

12.3 Secondary Study Outcome Measures

12.3.1 Patient Reported Toxicities

Patient reported toxicity data will be collected via Carevive surveys weekly for the first 12 weeks and then every other week for another 36 weeks. The questions will be from the PRO-CTCAE which is a patient-reported outcome measure developed to evaluate the toxicities that clinical trial subjects experience [10]. We will not deliver the PRO-CTCAE in its entirety but will specifically ask about the following common toxicities that are experienced with oral targeted therapy and immunotherapy: diarrhea, nausea, vomiting, fatigue, hand/foot syndrome, rash, abdominal pain, anorexia, mouth sores, cough and shortness of breath.

12.3.2 Clinician Reported Toxicities

Toxicities will also be formally assessed in-office every 3-4 months after commencement of a new targeted therapy/immunotherapy at routine follow-up visits. The clinician will assess several categories and rank them according to the CTCAE. The CTCAE are a set of criteria designed to standardize the adverse effects of cancer drugs for clinical trial purposes [26]. The categories chosen are common toxicities that occur with oral targeted therapy and immunotherapy: diarrhea, nausea, vomiting, fatigue, hand/foot syndrome, rash, abdominal pain, appetite, mouth sores, cough and shortness of breath

12.3.3 Quality of Life

Subjects will be asked to fill out the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-DRS) at baseline and approximately every 3 months in-office on a tablet device, with the help of the study team if needed. The FKSI-DRS is a 15-item index of the most important symptoms and concerns of people with advanced kidney cancer which has been determined to be reliable and valid when used in this setting [27].

12.3.4 Distress Level

The subject will be asked to rate their distress level in-office using the NCCN Distress Thermometer and Problem List for Patients [28], which is a 1 to 10 numerical scale. This will be delivered during routine office visits approximately every 3 months on a tablet.

12.3.5 Drug Adherence

The subject's drug adherence will be measured in the monthly survey using a three-question scale, and will also be determined through the subject's medication refill history. The subject's medication refill history will be obtained through their electronic medical record at the end of the study or at time of withdrawal.

12.3.6 Health Care Utilization

The subject's health care utilization will also be assessed by two measures. First, every four weeks via the Carevive survey, the subject will be asked about hospitalizations, emergency or urgent care visits, and unanticipated office visits to their primary care provider in the past month. At the end of the study or at time of withdrawal, a search of the electronic medical record will be performed to determine the number of calls made to oncology care providers and the number of visits to the oncologist.

12.3.7 Baseline Characteristics

Demographic (e.g. age and race) and relevant medical data (e.g. cancer diagnosis, treatment history, pre-existing co-morbidities) will be collected at the baseline visit. The study team member will obtain information necessary to complete these forms from the subject's electronic medical records when the subject is unable to provide this information in sufficient detail (e.g., staging, surgical procedures, types and doses of treatments).

13.0. CONFIDENTIALITY OF DATA AND DATA STORAGE

13.1 Utilizing Carevive Software for Symptom Monitoring.

Several steps will be taken to ensure that participant confidentiality is maintained throughout the study to the best of our ability. Patient reported symptom data will be collected via a Carevive software which complies completely with HIPAA standards. No Carevive software will be loaded on to cancer center devices. The Carevive platform will run in a web browser using Secure Sockets Layer (SSL) for managing the security of message transmissions over the Internet.

All questionnaires will be de-identified and reflect only the study-specific identification number of the participant. All self-reported questionnaires will be administered electronically using the Research Electronic Data Capture (REDCap) system.

13.2 Utilizing Research Electronic Data Capture (REDCap) and Information for Integrating Biology and the Bedside (i2b2)

Quality of life data will primarily be collected electronically via a web-based survey administered using Research Electronic Data Capture (REDCap) software. REDCap is a secure, web-based application for building and managing online surveys and databases and is made available free of cost through the University of Rochester Clinical Translational Science Institute. All data forms will be checked immediately by the REDCap system as they are being completed by the study participant to ensure completeness (i.e., that no question was skipped unintentionally), and a pop-up message feature will be used to encourage a response. Once data collection is complete, REDCap provides an automated export procedure for data download. Every effort will be made to reduce attrition and obtain follow-up data. Steps will be taken to avoid missing data, including careful instructions, and offering assistance.

Informatics for Integrating Biology and the Bedside (i2b2) will be used to help extract data from the electronic medical records. Specifically it will collect physician CTCAE ratings. The i2b2 clinical data query tool is made freely available to researchers at the University of Rochester (UR) through the leadership of the Clinical and Translational Science Institute (CTSI) and the UR Medical Center Information Systems Division. i2b2 is an open source informatics framework developed by the NIH-funded i2b2 Center at Harvard University to enable researchers to query clinical data from multiple clinical systems for research purposes. Through an easy-to-use graphical user interface, the i2b2 tool has the ability to perform a variety of queries for the purposes of cohort identification to support study feasibility, volunteer subject recruitment, and data visualization. Some examples of data currently available include patient demographics, diagnoses, medications, procedures, providers, laboratory results, microbiology results, patient questionnaires, and social history. De-identified data is available for study feasibility assessment and planning. With proper IRB approvals, users may

request identified data in the form of a user-specific i2b2 project, which can be exported for analysis.

The University of Rochester has developed a complementary tool to automate the process of moving clinical information from i2b2 to REDCap using an innovative graphical user interface. Researchers may use the tool to map clinical data in i2b2 to specific fields in a REDCap project using an application programming interface (API). With proper human subject approvals, identifiable information is available. Once in REDCap, information may be manipulated further, combined with other data collected outside the electronic health record system, and exported for analysis.

13.3. Data Storage

All hardcopy research records will be stored onsite in the University of Rochester Medical Center, in the Cancer Control Unit of the James P. Wilmot Cancer Institute, in an office suite secured by electronic key cards. Offices within the unit are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the University of Rochester Medical Center's password secured and firewall protected networks. These are the same methods of security used for patient medical records. All study data will be kept for a period of at least 6 years after the study and all reports and publications are complete. Carevive's electronic records will be compiled on their secure server for the duration of the study and transferred to the University of Rochester on completion of the study. They would only retain de-identified data on their server after the close of the study.

13.4. Assignment of Study ID

The study team will assign a numerical Study ID to each participant once they have agreed to participate in the study. Study forms and questionnaires will use this number and the participant's first and last initials as identifiers to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with study ID, name, and contact information will be maintained separately for the purpose of contacting participants if necessary; this database will be maintained until the study is closed. This linkage information will only be accessible to the study chair, study investigators, and the individual responsible for maintaining the database.

14.0. RESEARCH INFORMATION IN MEDICAL RECORDS

Documentation of study participation will be included in the medical record by means of uploading a signed consent form to each cancer survivor's medical record, for those participants enrolled in the research study from Wilmot Cancer Institute/University of Rochester Medical Center. Additionally, the subject's CTCAE results will be recorded in the chart at their visit approximately every 3 months. No further research-related information will be included in the medical record.

15.0. DATA ANALYSIS AND MONITORING

15.1 Primary Outcomes:

Primary Aim 1: *To evaluate the feasibility and usability of symptom monitoring and management with Carevive software*. Specifically, we will determine the demand for this intervention by calculating the rate of compliance. For example, in the case of monthly compliance, the

proportion of subjects who log in at least once during this time frame will be reported. The threshold criteria for compliance based on previous studies [29-30], will be a monthly compliance of 75% (ie. during each month, an average of at least 75% of the subjects completed at least one Carevive survey). Compliance will be determined for both survey completion and access of generated care plans. A sample size of 50 subjects produces a two-sided 95% confidence interval with a width of 0.254 for a point estimate of 75% compliance. Separately patient-level compliance will be determined, based on the proportion of logins that the subject completed during the course of the study. Reasons for noncompliance will be elicited at their subsequent login and will be reported descriptively.

Patient-rated usability, based on their SUS survey results, will also be employed as a measure of feasibility. This survey will be administered to subjects at the end of the study. A Score of >68 indicates greater than average usability [25]. We will determine overall mean usability scores, and we can produce a 95% confidence interval for the mean with a width of 0.57 standard deviations, utilizing the sample of 50 subjects.

We will also determine potential implementation obstacles for Carevive software by asking patients who fail to consent to the study to provide their reasoning. This will be reported descriptively. We will also keep track of the proportion of patients who are approached who fail to consent.

15.2 Secondary Outcomes:

Primary Aim 2: To *determine how patient-reported toxicities correlate to the subject's quality of life, distress level, drug adherence, health care utilization and physician reported toxicities.* Grading of each symptom and numeric values for quality of life, distress level, drug adherence and health care utilization rate will be determined as described in the "Data Collection and Monitoring Section." The strength of the association between symptom grade and each outcome will be measured using the Spearman's rank correlation coefficient.

Week		0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	Treatment D/C
PR-Symptoms	PRO-CTCAE Carevive survey	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PR-Healthcare Utilization	Carevive survey ?s					X				X				X		X		X		X		X		X		X		X		X		X	
PR- Drug Adherence	Adherence ?s Carevive survey					X				X				X		X		X		X		X		X		X		X		X		X	
Software Utilization	Carevive collected data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Care plan Utilization	Carevive collected data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Consent Failure	Recorded on screening log	X																															
Quality of Life	FKSI-DRS in office	X												X						X						X						X	
Distress Score	Distress Thermomer in office	X												X						X						X						X	
Usability	SUS																															X	X
CD-Symptoms	CTCAE	X												X						X						X						X	
CD-Healthcare Utilization	Electronic Medical Record																															X	X
CD- Drug Adherence	Pharmacy Confirmed																															X	X

Abbreviations: CD = Clinician Determined , PR = Patient Reported, PRO = Patient Reported Outcomes, CTCAE = Common Terminology Criteria for Adverse Events, FKSI-DRS = Functional Assessment of Cancer Therapy- Kidney Symptom Index- Disease related Symptoms, SUS = System Usability Scale

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