EXAMINING THE BURDEN OF TREATMENT WITHIN CANCER PATIENTS WITH MULTIMORBID CONDITIONS

By

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ABSTRACT

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The purpose of this dissertation was to examine the concept of burden of treatment (BOT), from both a conceptual and operational perspective, within cancer patients with multimorbid conditions. BOT is the combination of a patient's workload to manage their conditions, and the patient's perspective of that workload and their conditions. Manuscript one was a conceptual analysis and development of a conceptual model focused on the BOT of cancer patients with multimorbid conditions. Manuscripts two and three were secondary data analyses that utilized data from a parent trial study. The parent trial was a multi-site, randomized controlled trial (RCT) that tested an adherence and symptom management intervention in cancer patients that were newly prescribed oral oncolytic agents (OOA) over 12 weeks.

Manuscript two examined patients' OOA acquisition, defined as the number of days from the time of initial prescription until patients received their drug. This manuscript also examined how baseline disease/treatment factors (OOA drug class) and healthcare system factors (insurance type, recruitment site, and OOA copay) might predict the time to acquisition. All 272 patients form the parent trial were included in manuscript two. The number of days to acquisition was collected from the patient during the baseline telephone interview. The sample was evenly split between males and females, had a mean age of 61 years (SD=12.2), and was primarily Caucasian (89%). Patients waited on average 9.73 days from the time of initial prescription to receive their OOAs (range 0-135 days). ANOVA results showed that those that had a copay waited longer to receive their OOA (P = .02). Additionally, there was a significant interaction effect between OOA drug class, insurance type, and OOA copay (P = .01). Simple interaction effects showed significant acquisition times for those prescribed kinase inhibitors, F (1, 114) =

6.709, *p* .01, and sex hormone inhibitors, *F* (1, 19) = 7.879, *p* .01, depending on the type of insurance and whether or not individuals had a copay.

Manuscript three operationally tested the conceptual model developed in manuscript one. This chapter examined the direct relationship between baseline antecedent characteristics and temporary stoppages of patients' OOA regimens. Additionally, BOT-indicator variables were examined for a moderation effect on this direct relationship. OOA regimen complexity was utilized for the patient workload component of BOT, while patients' rating of their symptom interference on daily activities was used for patient perspective. More than 36% of patients in the parent trial experienced a temporary stoppage of their OOA regimen over 12 weeks. The moderation, interaction terms between BOT and multimorbidity were statistically non-significant. However, females (*P* = .02) and those prescribed kinase inhibitors (*P* < .01) were more likely to experience temporary stoppages when compared with males and other OOA drug classes, respectively.

Burden of treatment is a recently developed concept that will be valuable to research and practice as the prevalence of individuals with cancer and multimorbid conditions continues to increase. An individual's BOT can be related to the tasks required of them to manage their conditions, as well as the perspective they have about these tasks and conditions. This dissertation provided conceptual insight into the BOT experienced by cancer patients with multimorbid conditions, as well as the negative outcomes they may experience if their burden becomes too great. Patients may experience long wait times to receive cancer treatment that is vital, given their critical disease status. Although non-significant, there was a descriptive trend of more multimorbid conditions being associated with a greater proportion of temporary stoppages, as well as sex and drug class having an impact on these treatment modifications. The current literature does not adequately describe the burden of treatment experienced by cancer patients. Future research and practice guidelines are needed to help identify and ease the burden of treatment that individuals with cancer and multimorbid conditions experience.

This work is dedicated to my parents, Steve and Lois Vachon, for their continued support in all endeavors that I have undertaken throughout my life.

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Parent Trial

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CHAPTER ONE: INTRODUCTION

Introduction

The Centers for Disease Control and Prevention (CDC) estimates that one in four US adults have at least one chronic condition; this prevalence increases to three in four adults over the age of 65 years.[1] As an individual ages, they are at risk of having more than one chronic condition, which is known as multimorbidity. Cancer is one of the top 10 most prevalent chronic diseases, as well as the second leading cause of death among adults in the US.[1,2] As advances in cancer treatment continue, individuals are likely to live longer, and are, conversely, at risk of developing other chronic diseases or developing cancer while already having another chronic condition.[3] The presence of both cancer and another chronic disease(s) presents unique challenges for patients, caregivers/families, and healthcare providers. The required tasks for these patients to manage their diseases are known as the burden of treatment.[4-7] Burden of treatment (BOT) is comprised of two primary components: 1) the workload of being a patient (i.e., the healthcare tasks required to manage one's condition(s)) and 2) the patient's perspective of that workload.[5] The components of BOT are necessary, in order to understand the patient experience when trying to manage multiple morbidities. Both the patient workload and patient perspective may have an impact on the patient and clinical outcomes, including quality of life, utilization of healthcare resources, and continuation of treatment.[4-9]

Burden of treatment is a developing concept that has yet to be examined within cancer patients with multimorbid conditions.[10-12] As cancer patients continue to live longer, and have a greater risk for other chronic conditions, research will be vital to examine how to empower this population to effectively self-manage their conditions as well as how to decrease adverse clinical events, such as hospitalizations. This research will focus on the BOT experienced by cancer patients who have been prescribed oral oncolytic agents (OOA) who also have to manage other chronic conditions in terms of four categories: patient factors, social factors, healthcare system factors, and disease/treatment-related factors. Three separate but

interrelated manuscripts were completed in order to examine burden of treatment within this population. This dissertation includes a conceptual manuscript and two data-driven manuscripts utilizing a secondary analysis of a parent, clinical trial study.

Background and Significance

Cancer

According to the American Cancer Society (ACS), more than 1.7 million individuals will be newly diagnosed with cancer in 2018, as well as an estimated 15.5 million individuals are living with cancer or have a personal history of cancer.[13] Although these numbers are staggering, cancer mortality has greatly decreased in the last several years. From the height of cancer mortality in 1991 to 2015, the mortality rate has since decreased by more than 26%.[13] Improvements to life expectancy within cancer patients are due in part to decreased cancer risk factors, such as decreased smoking rates, better detection methods, and advances in available treatment.[3,14] Treatment advances, such as OOAs, have allowed oncology providers to better target cancer cells and specific genetic mutations.[15,16] The goal of newly-developed treatments is to increase length of survival and quality of life within cancer patients. As these survival rates continue to improve, there will be a greater need for the development of interventions to help cancer patients manage the workload brought on by their complex cancer treatment. With improved cancer survival rates, and longer life expectancies in the overall US population, the combination of cancer and other chronic diseases can bring about a more diverse array of healthcare tasks for patients and healthcare providers to manage

Oral Oncolytics

One form of cancer treatment being prescribed more frequently are OOAs. Halfdanarson and Jatoi indicated that in 2010, 10% of all chemotherapy medications prescribed were oral agents.[17] Bassan et al. reported in 2014 that 20–25% of all chemotherapy treatment was administered orally.[18] These statistics indicate oral oncolytic usage increased 15% in only four

years. This upward trend of OOA use will likely continue due to the large number of oral chemotherapy medications awaiting FDA approval.[19,20]

With recent treatment advances, such as OOAs, cancer has become a chronic disease requiring life-long treatment.[21,22] This paradigm shift in cancer treatment—from intravenous (IV) chemotherapy to oral agents—presents new obstacles for providers and patients. While IV chemotherapy administration is managed in a controlled environment by trained healthcare professionals, oral agents lack such firsthand monitoring, thereby shifting treatment responsibility to patients and their families, thus increasing the patient workload.[20] These oral regimens can be quite complex, being comprised of multiple oral medications with varying dosages, cycles (days on and days off), and special instructions (e.g., avoid certain medications or food).[23] These complexities are only taking into account the requirements to self-administer the OOAs.[4-9,22] Patients are also required to manage the symptoms and side effects brought on by their OOA regimens, which patients may not be adequately prepared for when self-administering cancer treatment in the home as opposed to receiving IV chemotherapy in the clinic.[15,18,22,24] Add to this another chronic condition that requires management and the workload and BOT may be multiplied, which can impact the patient's perspective of their disease and ability to manage multiple chronic conditions.

With the introduction of oral oncolytics, the delivery of cancer care has changed significantly, with management responsibility shifted from healthcare providers to patients and caregivers.[15,24-26] The most commonly discussed topics in the literature regarding oral oncolytics are medication management, symptom and side effect burden, and financial concerns.[18,21,27-33] Properly managing oral oncolytics is crucial for reducing disease progression, maintaining functionality and quality of life, and preventing premature death.[15,16,23,25,34,35] However, several factors make managing oral oncolytics difficult. These factors fall into the following four categories: patient, social, healthcare system, and disease/treatment-related factors.[23] This dissteration focuses on components of these four categories, but will emphasize the

disease/treatment and healthcare system factors in relation to cancer patients with multimorbid conditions. Having an additional chronic disease can impact the amount of work that an individual must complete to control their conditions. This increased workload from other conditions may affect an individual's ability to manage their cancer treatment, especially oral oncolytics. Healthcare system factors can make it difficult for patients to adequately manage their cancer treatment when prescription errors, difficulties with insurance coverage, and slow delivery by specialty pharmacies delay patients acquiring their oral oncolytics.[36-38] These factors contribute to the BOT and its impact on cancer patients' treatment course.

Due to the differences in cancer types and drug classes, the majority of the oral oncolytic literature does not isolate specific side effects unless the study examined a single drug. However, the most common side effects noted in the literature are diarrhea, nausea, skin complications (e.g., rash, blisters, or dry skin), oral mucositis, fatigue, sleep disturbance, and neuropathy. [15,19,28,33,39] Because most cancer and multimorbidity management takes place in the home, it is imperative that providers have open communication with patients to provide education and keep patients informed about possible side effects and management strategies, as well as to monitor how patients are doing. Unmanaged side effects may require the need for dose modifications, medication interruptions, a switch to IV agents, discontinuation of cancer treatments, or utilization of healthcare resources.[40-42]

Patients may face financial difficulties due to out of pocket (OOP) costs of OOAs, which can total several thousand dollars per month.[37,43-45] Additionally, difficulties with insurance coverage and the need to use specialty pharmacies can lead to patients discontinuing or delaying necessary cancer treatments.[33,38,45,46] Whether it is having to pay for their OOAs or manage the symptoms and side effects, OOAs add to the workload of being a cancer patient by requiring more responsibility of the patient.[36] The challenges accompanied by OOA regimens and symptom and side effect management may be further exacerbated for patients who have multiple chronic conditions that also require complex management.

Multimorbidity

Multimorbidity, or the presence of multiple chronic conditions, has become more common for individuals than any single chronic condition in the United States.[47] Researchers estimate that by the year 2020, 81 million people will be suffering from multimorbidity,[48] a condition that can be difficult for healthcare providers and patients to manage. The American Association of Retired Persons (AARP) estimates that more than 50% of those over 65 years old with cancer have multiple chronic conditions.[49] Multimorbidity has been associated with decreased patient functionality and quality of life, increased healthcare utilization, exacerbation of chronic conditions, and increased mortality.[50] Despite its prevalence, the cancer literature has only recently included multimorbidity. One reason for this lack of attention is the strict eligibility criteria of cancer treatment drug trials. Most patients with other chronic conditions, especially older adults, are not eligible for these drug trial studies due in part to the possible interaction of the other prescription drugs with the trialed medications.[3,14] Within the limited literature, multimorbidity in cancer patients has been associated with higher rates of complications and side effects, decreased quality of life, increased disability, higher healthcare spending, greater financial burden, and decreased survival.[4,8,9,50] Due to this limited evidence, it has been difficult for providers to develop evidence-based care and treatment plans for cancer patients with multimorbidities. Treatment plans have been primarily centered around a single-disease approach, as opposed to focusing on both cancer and other conditions.[3]

The existing cancer multimorbidity literature includes studies in which researchers inquire about cancer patients' other conditions and examine correlations between the other chronic conditions and cancer.[12,51] However, no BOT studies were identified that specifically target cancer patients with multimorbid conditions. The topic of cancer patients with multimorbid conditions taking an oral oncolytic has also not been addressed. While the number of individuals with cancer and other conditions is expected to increase, along with their use of OOAs, the pace of research with this population lags behind what it should be.

Without studies specifically targeting cancer patients with multimorbid conditions, understanding their BOT and developing interventions to empower patients to manage their diseases cannot happen. This dissertation lays the foundation for a program of research focused on examining the increased BOT experienced by individuals with cancer and other chronic conditions, with the goal of developing interventions to equip these patients to manage their burden of treatment more effectively.

Burden of Treatment

Burden of treatment is the combination of patient workload and patient perspective. Patient workload is the required tasks needed for patients to manage their conditions. While, patient perspective is the way in which patients perceive their workload and conditions. Burden of treatment has only been a topic of discussion within the last decade, with the continued rise of chronic conditions and multimorbidity.[4-7,10-12,50,52-57] The development of this concept was needed in order to articulate the work that must be done by patients to manage their chronic conditions.[4,6] BOT as a concept has become important due to the shift to shorter inpatient stays and a greater emphasis on patient self-management in the home. This emphasis on self-management has led to patients being more responsible for their care, and therefore a greater workload, or burden, may be imposed upon them. Tran, Sav, and Eton are the three primary contributors to the development of BOT literature. Their work began with the conceptualization of BOT and has transitioned to developing empirical BOT measures for use within certain chronic disease populations.[5,6,9]

Along with chronic conditions[55,56] in general, and multimorbidity,[50] BOT, as a concept, has been utilized within specific chronic conditions, including HIV/AIDS,[52,54,58] mental illness,[15,17] diabetes,[59] cardiovascular diseases,[60] cystic fibrosis,[53] hyperlipidemia,[55] asthma,[6,55] and stroke.[9,55] These chronic condition studies have varied in design, predictor variables, and outcomes, although outcomes have been seldom analyzed as most studies have been exploratory. For the qualitative studies, researchers examined themes surrounding BOT within

their population of interest.[4,7,55,57] These themes are discussed later in this dissertation within the components of burden of treatment. While some studies have discussed BOT from a conceptual standpoint through literature reviews,[5,52,54] the quantitative studies have supplemented indicator variables in order to better understand components of BOT. As opposed to utilizing a BOT specific measure, these works included variables that acted as a substitute. Indicator variables were used that are components of BOT as opposed to a validated BOT-specific measure. These indicator variables have consisted of treatment complexity,[53,55] number of medications,[54,57] number of interactions with healthcare providers,[10-12] and difficulty managing treatment.[55-57] Due to the use of indicator variables as opposed to BOT-specific measures, it can be difficult for researchers and clinicians to utilize BOT literature, especially for cancer patients where BOT has only been a recent focus.

Three studies were found to center around the concept of BOT within cancer patients. Two of the studies utilized data from national databases, Surveillance Epidemiology and End Results (SEER-Medicare)[12] and an institutional cancer registry,[10] while the other study recruited patients through a national survey registry and had direct contact with participants.[11] These studies evaluated burden based on the number of days interacting with the healthcare system,[10-12] type of interaction (e.g., receiving cancer treatment, clinic visit, or ER/acute stay),[10-12] number of physicians the patients were interacting with,[12] number of medications,[12] and symptom burden.[11] Only one of the studies measured and included multimorbidities within their analysis.[12] Presley et al. found that those with a greater number of multimorbid conditions were more likely to experience a higher BOT, as measured by interaction time with the healthcare system and number of prescription medications. Although these measures are primary components of BOT, these variables do not begin to tell the complete story for these cancers patients because they do not describe all of the healthcare activities patients needed to complete or convey how patients perceive the difficulties and complexities with these tasks.

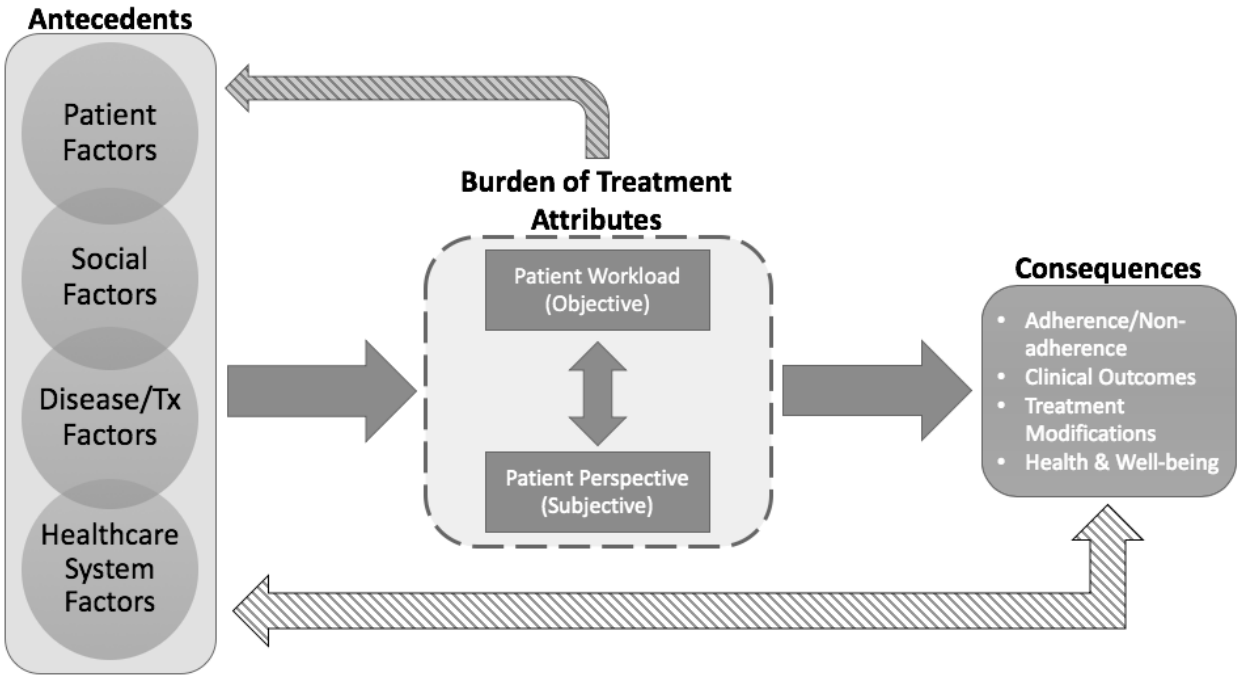
The lack of research examining patients' perspective of their workload has been the continued challenge for researchers undertaking BOT work with any chronic disease population.[4,5,7] The current BOT literature within cancer patients has only utilized indicator variables to understand the concept of BOT. This work, being a secondary data analysis, will do the same, while future works in this program of research will utilize BOT-specific measures within cancer patients with multimorbid conditions. Although this study will utilize multiple indicator variables, it provides preliminary data and lays the foundation for future studies empirically measuring BOT, and ultimately developing strategies and interventions to combat the daily challenges faced by cancer patients with multimorbid conditions.

Conceptual Model

This dissertation is driven by a derived theoretical model called the Burden of Treatment Morbidity (BOTM) Model, which is essential in guiding this work and future studies within this program of research. The BOTM (Figure 1) is derived from the work of three primary contributing research teams to the BOT literature and the concept analysis that will be discussed in chapter 2.[4-9] Tran, Sav, Eton, and their teams have laid the foundation for BOT literature through their conceptual framework development. Similar to Sav et al.,[5] the BOTM follows Rodger's evolutionary concept analysis method.[61,62] The BOTM works to explain how BOT impacts the daily life of an individual with chronic disease(s). The model begins with the four antecedent categories of factors that precede BOT, which were mentioned earlier in the chapter (patient, social, healthcare system, disease/treatment). These factors directly impact the attributes of burden of treatment, as well as the consequences, much like a mediation model. Additionally, there are feedback loops from the attributes of BOT and the consequences back to the antecedents. These feedback loops illustrate the dynamic nature of BOT, as the different components have the potential to be continuously changing and impacting one another. The ensuing sections will lay out the three primary components of the BOTM (antecedents,

attributes, and consequences), as well as describe the directional relationships of the components.

Figure 1.1. Burden of Treatment Morbidity (BOTM) Model



Attributes

Burden of treatment is comprised of two primary components: patient workload and patient perspective.

Patient Workload. As exemplified by the standard definition of burden of treatment, "the workload of being a patient," BOT is primarily viewed within the context of the required tasks that individuals must undertake in order to manage their chronic disease(s).[4-7] These activities will vary depending on the disease population and the individual patient. However, the most commonly discussed activities break down into the following categories: learning about one's disease, medication management, nonpharmacological/equipment management (e.g. CPAP machine), symptoms and side effects management, lifestyle changes (e.g. diet and exercise),

healthcare system interactions, and financial responsibilities.[4-7,10-12,50,52-57,63] Different tasks are encompassed by these overarching categories and will be influenced by certain antecedents, such as disease or treatment factors and healthcare provider decisions. Dependent upon the quantity and complexity of these tasks, as well as some individual and social characteristics (e.g. marital status), patients may view their workload as stressful or overwhelming, and this stress may impact their ability to manage their disease(s) and their overall quality of life.[5] The patient workload can change depending on the number of diseases that an individual has, as well as the complexity of the treatment regimens to manage these diseases. One would anticipate that those with more chronic diseases and subsequent treatment will have more tasks to complete in order to manage these diseases.[4,5,7,9]

Patient Perspective. The patient perspective is how an individual perceives their disease(s) and the tasks needed to manage their illnesses. The three primary BOT contributors discussed the Normalization Process Theory (NPT) as influencing their conceptualization of BOT.[4,5,7,](cite NPT). The NPT focused on the integration of practices into an individual's or group's everyday routine. For individuals with chronic disease, NPT applies to the need to integrate healthcare tasks into everyday life in order to manage their disease. One component of the NPT, "reflexive monitoring," focuses on the subjective viewpoints of individuals and groups when integrating practices and tasks into everyday life. Reflexive monitoring specifically examines how individuals and groups evaluate and mentally process the impact of integrating practices into life. Reflexive monitoring provides an underpinning for the subjective patient perspective within the concept of BOT, and how individuals with chronic diseases perceive their diseases and associated workload.

Patients may have negative reactions, such as fear, anger, and distress, which may negatively impact their outcomes. However, when researchers or clinicians are able assist patients in adapting their illnesses perceptions, patients are able to improve self-management and recovery from acute adverse events.[68,69] As the patient workload changes, so can the

patient perspective. With the addition of a chronic condition, the patient workload changes; therefore, the patient perspective changes with the new paradigm. This change in perspective may be positive or negative, depending on the intensity of the workload change and how difficult it may be for the patient to adapt.[5,6] The goal in measuring this component of BOT is to understand patients' perspective about their illness and the associated workload to be able to positively alter these perceptions and empower patients to effectively self-manage their diseases. Before the two components of BOT can be examined, there are preceding factors that must take place. These preceding factors are known as antecedents.

Antecedents

Antecedents are the four preceding categories of factors (patient, social, healthcare system, disease/treatment) that must occur before the examination of BOT can begin.

Patient Characteristics. Depending on the disease population, patient demographics can have a substantial impact on BOT and the associated outcomes. Age, sex, race, socioeconomic status, employment status, and education level can all have an impact on burden,[4-6,50,54] either through biological processes or by having the knowledge and resources available to receive quality care. Patients' functional status, whether physical or cognitive, also plays a role on how patients are able to adapt and manage their disease(s).[70-73] A major patient characteristic that may impact burden is the patients' psychological status, such as having anxiety or depression.[74-79] This is not the same as the patient perspective, but one's psychological wellbeing can frame an individual's perspective on their disease(s) and the associated burden, as well as impact their ability to adapt and be resilient to that burden. For example, an individual with depression or anxiety may have a more difficult time adapting to a higher workload, therefore increasing their level of distress. The patient perspective and ability to reframe the situation are truly the keys to the level of impact that burden of treatment may have on a patient's health and overall quality of life.

Social Factors. Family and friends are often associated with helping patients through difficult times. Patients having increased social support can lead to a lower burden of treatment, if their loved ones are able to assist in managing some of the healthcare tasks.[80-84] However, the sense of burden can also go the other way. Some patients feel an increased burden if they believe that they, and their disease, are having a negative impact on the lives of their loved ones.[5,9] It is important to understand the social dynamic of individuals with chronic disease, and the impact the patients feel their support system (i.e. spouse and family members) has on them, but also their perception of how their disease(s) impact the lives of those around them.

Disease/Treatment Factors. When working with BOT, the issues surrounding disease and treatment factors may be the most influential, as well as the most difficult, to control for patients. Especially when working with multimorbid individuals, the difficulties managing diseases with multiple associated treatments can be a daunting task. When there are interactions among diseases and/or medications, management of diseases and treatment can become even more difficult, even impossible, for patients to self-manage, requiring intervention from healthcare providers.[4-6,21,50] For example, an individual with cancer and diabetes may be prescribed an oral oncolytic combined with a corticosteroid, which has a common side effect of elevated blood sugars. This cancer treatment regimen presents a new challenge for a cancer patient to manage, but they also need to worry about how the cancer treatment may affect their diabetes and their ability to manage their diabetes. In addition, those with cancer face particular challenges with constant changes to treatment regimens, especially dose reductions and temporary stoppages with OOAs.

With the shift towards outpatient care and increased management in the home, patients are being tasked with a greater responsibility of self-management. However, patients may not have the knowledge or confidence to understand how to effectively manage the competing characteristics of multiple diseases and their treatments, which can impact the patient perspective and their overall burden. In the earlier example, the patient may not be aware that

steroids can impact their blood sugars. The patient must rely on their oncologist or nurse to know that they have diabetes and are being prescribed a steroid. The oncologist or nurse will thus be able to work with the patient to develop or modify strategies to manage their disease and associated treatment. This example illustrates how one added medication or the diagnosis of a new chronic disease can have a substantial impact on the patient and their ability to manage their multiple chronic conditions. The increased number of healthcare tasks, combined with the overwhelming responsibility, leads to an increased burden among individuals with cancer and other chronic conditions.[4,7,10,12,50,56,57]

Healthcare System Factors. Although more responsibility is being placed on the patient to manage their chronic disease(s), the healthcare system plays a substantial role in patients being successfully able to effectively self-manage in the home.[6,11,52] The healthcare system must do a great deal of work at the onset to educate and prepare patients before they are ready to take control of their disease and treatment regimen. Adequately preparing patients to self-manage their conditions is made possible through effective education and open communication between providers and patients. Patients must trust their provider and feel that their voice is heard, or they are less likely to act on the advice from their providers.[85-88] Lack of patient-provider communication or too much being asked of patients can be stressful and lead to an increased burden for patients. Patients may experience increased stress when having extended wait times to schedule appointments with specialists, such as oncologists. Looking specifically at oral oncolytics, acquisition of OOAs may be made difficult due to delayed insurance approvals because of rising costs,[37,38] increased regimen changes may bring about prescription errors,[38] and waiting for a specialty pharmacy to fill or ship the prescription. OOAs are not as readily available to patients as most other medication, and it can therefore be stressful for patients with late-stage disease waiting to receive a critical medication.[4,6,38] Patients need to be able to trust the healthcare system and feel their needs are being addressed, or the foundation of their disease management begins to break down.

Summary

This model adds to the existing literature by displaying the interactive and dynamic relationship of patient workload and patient perception, the primary components of BOT. The BOTM also shows how the different components of the model interact with one another, either having a direct or indirect impact. The antecedent categories may have a direct impact on the consequences or may have an impact on burden of treatment, which then impacts the consequences. At the same time, BOT has a feedback loop with the antecedent categories, as does the ultimate consequences. What the BOTM shows is the chronic disease and BOT process is dynamic, and therefore constantly changing. When a decision is made by the patient or the healthcare provider, or a new medication or lifestyle change is added to the list of tasks needed to be completed, all aspects of the model have the potential to be impacted, especially the patient perspective. This model helped guide this work to better describe the BOT faced by cancer patients with multimorbidities. It also serves as the foundation for a future program of research focused on empowering this population to take control of their diseases and ease their burden of treatment.

Purpose

The purpose of this work is to examine burden of treatment from multiple viewpoints among cancer patients with multimorbid conditions. This three-part dissertation 1) describes BOT from a conceptual standpoint; 2) describes the healthcare system factors that impact patient acquisition of OOAs; and 3) examines how BOT may moderate the relationship between cancer patients' antecedents and their continuation on their cancer treatment. These three parts are distinct manuscripts that share common themes throughout to create one synchronized dissertation. This work begins to address a number of gaps in both BOT and cancer literature. It examines BOT in cancer patients with multimorbid conditions conceptually, which has not been done for this specific population. This work also uses indicator variables for BOT, which is common in the current literature, but this work examines BOT's impact on cancer patients'

continuation of care, which has not been previously done analytically. This dissertation work lays a foundation for a program of research focused on developing strategies and interventions to empower cancer patients with multimorbid conditions to effectively self-manage their cancer and other disease(s).

Dissertation Format

Due to the continued emphasis placed on production and manuscript publication, this dissertation follows the three-manuscript approach. The dissertation is a secondary analysis of a parent trial study[89] focused on management interventions for cancer patients newly prescribed OOAs. As previously mentioned, the three manuscripts are as follows: 1) a conceptual analysis examining the burden of treatment among cancer patients with multimorbid conditions; 2) a data-driven paper describing the time from prescription to patient receipt of OOAs and what healthcare system variables might predict this acquisition time; and 3) a moderation analysis examining how the burden of treatment of patients in the parent study may impact the relationship of baseline antecedents and consequence of patients continuing on their cancer treatment.

Chapter 2 will present a concept analysis manuscript that utilizes Rodger's evolutionary concept analysis process.[61,62] This chapter involves an in-depth discussion of BOT and the Burden of Treatment Morbidity Model. The paper will be in the context of cancer patients with multimorbid conditions and the challenges faced by these patients, as evidenced by the literature. This concept analysis is not limited to those cancer patients that have been prescribed OOAs, but includes all cancer patients that also have other chronic disease(s) that require treatment. The primary focus of this chapter is on the concept of BOT within the specific population. This paper will plan to be submitted to the Journal of Advanced Nursing, as this journal is one of the primary publishers of concept analysis works in the nursing literature.

Chapter 3 will be a secondary data analysis describing the healthcare system factors that have impacted patients' acquisition of their oral oncolytic agents. The secondary analysis

was of a parent trial, which focused on management interventions in patients that were newly prescribed OOAs. For this work, acquisition was the time from OOA prescription to patient receiving the medication.[90] The following variables were utilized:

- Antecedents: Healthcare system: insurance type (government/private), OOA copay (yes/no), and patient recruitment site. Disease/Treatment: OOA medication class.
- Consequence: time to acquisition of OOA (amount of time from initial prescription until the patient receives their OOA).

Chapter 3, first, descriptively examines the time to acquisition for patients' oral oncolytics. After describing the time to acquisition, analysis of variance was utilized to analyze how insurance type, whether patients have a copay for their OOA at initiation or not, patient recruitment site, and OOA medication class might predict the time to acquisition.

Chapter 3 also includes some qualitative work within the patient interview call logs, in order to identify specific examples of patients experiencing an error or delay by the healthcare system in acquiring their OOA. Some examples may be prescriber errors, insurance delays, pharmacy errors, or specialty pharmacy shipment delays. These examples are included in the discussion to provide examples of real patient experience in acquiring their oral agents for clinicians and researchers to consider during clinical practice and future research.

Chapter 4 is a secondary data analysis examining the relationship between baseline antecedents, BOT variables, and continuation of cancer treatment. The secondary analysis is from the same parent study as Chapter 3. It is hypothesized that there are relationships between baseline antecedents and consequences experienced by cancer patients, thus BOT was tested as a moderating variable of this hypothesized relationship. Although the parent study did not include a specific BOT measure or scale, indicator variables were used that were included in the parent trial study. This chapter utilizes the following variables from the parent trial:

- Antecedents: patient—age, sex, and employment status (employed/not employed). Social: marital status (married/single). Healthcare system: insurance type (government/private) and OOA copay (yes/no). Disease/Treatment: number of chronic conditions (other than cancer) and class of OOA.
- Burden of treatment: cancer treatment regimen complexity, as measured by the modified medication regimen complexity index,[91] and the level of daily interference from cancer symptoms at baseline.
- Consequences: temporary stoppages in the patient's cancer treatment protocol will be utilized for continuation of care. A temporary stoppage will constitute any added delay in the treatment protocol, which was not part of the prescribed regimen. Due to insufficient counts at each time period of the parent trial study, temporary stoppages were measured by whether or not an individual experienced a temporary stoppage or not over the course of the entire trial.

A moderation logistic regression analysis was utilized to describe how the BOT indicator variables moderate the relationship between the antecedents and the consequence of temporary stoppages of patients' oral oncolytic regimens. All of the antecedent and BOT variables were baseline measures, while the temporary stoppages were over the course of the trial. Because the emphasis of this dissertation is focused on the added burden of treatment by multimorbid conditions on cancer patients, the BOT moderation variables were added into the model as interactions with the multimorbid conditions antecedent variable. There were two moderation models, because there are two separate BOT-indicator variables that are being considered as moderators (symptom interference and cancer treatment regimen complexity).

Chapter 5 will summarize the findings of the three manuscripts as individual papers, as well as the themes that tie them together. The final chapter also discusses the gaps addressed by the overall work, limitations of the dissertation study, and the future studies that will be

included within this program of research and how they will contribute to the nursing and oncology literature. This section also discusses the implications these papers have on research, practice, and policy within the healthcare setting and in the patient home.

REFERENCES

REFERENCES

1. CDC. Chronic Disease 2017; https://www.cdc.gov/chronicdisease/index.htm

2. CDC. Leading Causes of Death. 2017; https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.

3. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin.* 2016;66(4):337-350.

4. Tran VT, Barnes C, Montori VM, Falissard B, Ravaud P. Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions. *BMC Med.* 2015;13:115.

5. Sav A, King MA, Whitty JA, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. *Health Expectations: An International Journal of Public Participation in Health Care and Health Policy.* 2013;18(3):312-324.

6. Eton DT, Elraiyah TA, Yost KJ, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. *Patient Related Outcome Measures.* 2013;4:7-20.

7. Eton DT, Ridgeway JL, Egginton JS, et al. Finalizing a measurement framework for the burden of treatment in complex patients with chronic conditions. *Patient Related Outcome Measures.* 2015;6:117-126.

8. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med.* 2014;12:109.

9. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC Med.* 2012;10:68.

10. Cheng AC, Levy MA. Data Driven Approach to Burden of Treatment Measurement: A Study of Patients with Breast Cancer. *AMIA Annual Symposium proceedings AMIA Symposium.* 2016;2016:1756-1763.

11. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer.* 2008;16(7):791-801.

12. Presley CJ, Soulos PR, Tinetti M, Montori VM, Yu JB, Gross CP. Treatment Burden of Medicare Beneficiaries With Stage I Non–Small-Cell Lung Cancer. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2016;13(2):398-e107.

13. ACS. *Cancer Facts and Figures, 2018.* Cancer.org: American Cancer Society 2018.

14. Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. *Journal of Geriatric Oncology.* 2016;7(4):249-257.
15. Arthurs G, Simpson J, Brown A, Kyaw O, Shyrier S, Concert CM. The effectiveness of therapeutic patient education on adherence to oral anti-cancer medicines in adult cancer patients in ambulatory care settings: a systematic review. *JBI Database of Systematic Reviews and Implementation Reports.* 2015;13(5):244-292.

16. Verbrugghe M, Duprez V, Beeckman D, et al. Factors Influencing Adherence in Cancer Patients Taking Oral Tyrosine Kinase Inhibitors: A Qualitative Study. *Cancer Nursing.* 2016;39(2):153-162.

17. Halfdanarson TR, Jatoi A. Oral cancer chemotherapy: the critical interplay between patient education and patient safety. *Current Oncology Reports.* 2010;12(4):247-252.

18. Bassan F, Peter F, Houbre B, et al. Adherence to oral antineoplastic agents by cancer patients: definition and literature review. *European Journal of Cancer Care.* 2014;23(1):22-35.

19. Salgado TM, Mackler E, Severson JA, et al. The relationship between patient activation, confidence to self-manage side effects, and adherence to oral oncolytics: a pilot study with Michigan oncology practices. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer.* 2017;25(6):1797-1807.

20. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK. Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review. *JAMA Oncology.* 2018;4(1):105-117.

21. Given BA, Spoelstra SL, Grant M. The challenges of oral agents as antineoplastic treatments. *Seminars in Oncology Nursing.* 2011;27(2):93-103.

22. Trivedi D, Landsman-Blumberg P, Darkow T, Smith D, McMorrow D, Mullins CD. Adherence and persistence among chronic myeloid leukemia patients during second-line tyrosine kinase inhibitor treatment. *Journal of Managed Care & Specialty Pharmacy.* 2014;20(10):1006-1015.

23. Hall AE, Paul C, Bryant J, et al. To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Critical Reviews in Oncology/Hematology.* 2016;97:247-262.

24. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. *Cancer Treat Rev.* 2014;40(1):102-108.

25. Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. *Cancer Treat Rev.* 2013;39(6):610-621.

26. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Research and Treatment.* 2012;134(2):459-478.

27. Accordino MK, Hershman DL. Disparities and challenges in adherence to oral antineoplastic agents. *American Society of Clinical Oncology Educational Book / ASCO American Society of Clinical Oncology Meeting.* 2013:271-276.
28. Arber A, Odelius A, Williams P, Lemanska A, Faithfull S. Do patients on oral chemotherapy have sufficient knowledge for optimal adherence? A mixed methods study. *European Journal of Cancer Care.* 2015;26(2):1-8.

29. Bourmaud A, Henin E, Tinquaut F, et al. Adherence to oral anticancer chemotherapy: What influences patients' over or non-adherence? Analysis of the OCTO study through quantitative-qualitative methods. *BMC Research Notes.* 2015;8(291);1-8.

30. Gandhi S, Day L, Paramsothy T, et al. Oral Anticancer Medication Adherence, Toxicity Reporting, and Counseling: A Study Comparing Health Care Providers and Patients. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2015;11(6):498-504.

31. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin.* 2009;59(1):56-66.

32. Kimura M, Nakashima K, Usami E, et al. Adherence and awareness of the therapeutic intent of oral anticancer agents in an outpatient setting. *Oncology Letters.* 2015;9(5):2341-2346.

33. Esper P. Identifying Strategies to Optimize Care With Oral Cancer Therapy. *Clinical Journal of Oncology Nursing.* 2013;17(6):629-636.

34. Mathes T, Pieper D, Antoine SL, Eikermann M. Adherence influencing factors in patients taking oral anticancer agents: a systematic review. *Cancer Epidemiology.* 2014;38(3):214-226.

35. Verbrugghe M, Timmers L, Boons CC, Van Den Bemt BJ, Hugtenburg JG, Van Hecke A. Adherence to oral anticancer agents: Healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands. *Acta Oncologica (Stockholm, Sweden).* 2016;55(4):437-443.

36. May P, Figgins B. Oral anticancer therapy: a comprehensive assessment of patient perceptions and challenges. *The Journal of Community and Supportive Oncology.* 2016;14(3):112-116.

37. Dusetzina SB, Huskamp HA, Winn AN, Basch E, Keating NL. Out-of-Pocket and Health Care Spending Changes for Patients Using Orally Administered Anticancer Therapy After Adoption of State Parity Laws. *JAMA Oncology.* 2017;4(6): e173598.

38. Niccolai JL, Roman DL, Julius JM, Nadour RW. Potential Obstacles in the Acquisition of Oral Anticancer Medications. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2017;13(1):e29-e36.

39. Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: the role of the midlevel practitioner. *The Journal of Supportive Oncology.* 2012;10(1):14-24.

40. Bardin C, Veal G, Paci A, et al. Therapeutic drug monitoring in cancer--are we missing a trick? *European Journal of Cancer (Oxford, England : 1990).* 2014;50(12):2005-2009.
41. Prasad V, Massey PR, Fojo T. Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2014;32(15):1620-1629.

42. Sachs JR, Mayawala K, Gadamsetty S, Kang SP, de Alwis DP. Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example. *Clinical Cancer Research: An Official journal of the American Association for Cancer Research.* 2016;22(6):1318-1324.

43. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2014;32(4):306-311.

44. Lee C, Grigorian M, Nolan R, Binder G, Rice G. A retrospective study of direct cost to patients associated with the use of oral oncology medications for the treatment of multiple myeloma. *Journal of Medical Economics.* 2016;19(4):397-402.

45. Kaisaeng N, Harpe SE, Carroll NV. Out-of-pocket costs and oral cancer medication discontinuation in the elderly. *Journal of managed care & specialty pharmacy.* 2014;20(7):669-675.

46. Thanki K, Gangwal RP, Sangamwar AT, Jain S. Oral delivery of anticancer drugs: challenges and opportunities. *Journal of Controlled Release: Official Journal of the Controlled Release Society.* 2013;170(1):15-40.

47. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. *JAMA.* 2012;307(23):2493-2494.

48. Suls J, Green PA, Davidson KW. A Biobehavioral [corrected] Framework to Address the Emerging Challenge of Multimorbidity. *Psychosomatic Medicine.* 2016;78(3):281-289.

49. AARP. Chronic Conditions Among Older Americans 2012. https://assets.aarp.org/rgcenter/health/beyond_50_hcr_conditions.pdf

50. Pefoyo AJ, Bronskill SE, Gruneir A, et al. The increasing burden and complexity of multimorbidity. *BMC Public Health.* 2015;15(415).

51. Von Ah D. Cognitive changes associated with cancer and cancer treatment: state of the science. *Clinical Journal of Oncology Nursing.* 2015;19(1):47-56.

52. Lepine JP, Briley M. The increasing burden of depression. *Neuropsychiatric Disease and Treatment.* 2011;7(Suppl 1):3-7.

53. Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society.* 2013;12(5):461-467.

54. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatric Services (Washington, DC).* 2014;65(8):977-987.

55. Ridgeway JL, Egginton JS, Tiedje K, et al. Factors that lessen the burden of treatment in complex patients with chronic conditions: a qualitative study. *Patient Preference and Adherence.* 2014;8:339-351.

56. Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. *The American Journal of Gastroenterology.* 2014;109(9):1304-1311.

57. Lhuilier D, Brugeilles F, Rolland D. Chronic disease and treatment burden for patients: the example of hepatitis C. *Sante Publique (Vandoeuvre-les-Nancy, France).* 2015;27(1 Suppl):S17-21.

58. Gao X, Nau DP, Rosenbluth SA, Scott V, Woodward C. The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS Care.* 2000;12(4):387-398.

59. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes care.* 2004;27(7):1535-1540.

60. Stange D, Kriston L, von-Wolff A, Baehr M, Dartsch DC. Reducing cardiovascular medication complexity in a German university hospital: effects of a structured pharmaceutical management intervention on adherence. *Journal of Managed Care Pharmacy : JMCP.* 2013;19(5):396-407.

61. Rodgers BL. *Concept Development in Nursing: Foundations, Techniques, and Applications.* 2nd ed. Philadelphia, PA: Saunders; 2000.

62. Tofthagen R, Fagerstrom LM. Rodgers' evolutionary concept analysis--a valid method for developing knowledge in nursing science. *Scandinavian Journal of Caring Sciences.* 2010;24 Suppl 1:21-31.

63. Boyd CM, Wolff JL, Giovannetti E, et al. Healthcare task difficulty among older adults with multimorbidity. *Medical Care.* 2014;52 Suppl 3:S118-125.

64. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *Journal of Psychosomatic Research.* 2006;60(6):631-637.

65. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. *Psychology & Health.* 2015;30(11):1361-1385.

66. Lau RR, Bernard TM, Hartman KA. Further explorations of common-sense representations of common illnesses. *Health Psychology: Official journal of the Division of Health Psychology, American Psychological Association.* 1989;8(2):195-219.

67. Leventhal H, Nerenz, D.R., & Steele, D.J. Illness Representations and Coping with Health Threats. *Handbook of Psychology and Health*. Hillsdale, NJ: Erllbaum Associates; 1984:219-252.

68. Petrie KJ, Cameron LD, Ellis CJ, Buick D, Weinman J. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosomatic Medicine.* 2002;64(4):580-586.

69. Petrie KJ, Broadbent, E., Meechan, G. Self-regulatory interventions for improving the management of chronic illness. *The Self-Regulation of Health and Illness Behaviour*. New York, NY: Routledge; 2003:257-277.

70. Arai Y, Hirose N. [Functional status, morbidity, and mortality of centenarians]. *Clinical Calcium.* 2013;23(1):45-50.

71. Banerjee D, Perry M, Tran D, Arafat R. Self-reported health, functional status and chronic disease in community dwelling older adults: untangling the role of demographics. *Journal of Community Health.* 2010;35(2):135-141.

72. Guaraldi G, Silva AR, Stentarelli C. Multimorbidity and functional status assessment. *Current \Opinion in HIV and AIDS.* 2014;9(4):386-397.

73. Ozturk A, Simsek TT, Yumin ET, Sertel M, Yumin M. The relationship between physical, functional capacity and quality of life (QoL) among elderly people with a chronic disease. *Archives of Gerontology and Geriatrics.* 2011;53(3):278-283.

74. Health NIoM. Chronic Disease & Mental Health. 2016; https://www.nimh.nih.gov/health/publications/chronic-illness-mental-health/index.shtml.

75. Kobau R, Zack MM. Attitudes toward mental illness in adults by mental illness-related factors and chronic disease status: 2007 and 2009 Behavioral Risk Factor Surveillance System. *American Journal of Public Health.* 2013;103(11):2078-2089.

76. Lin WC, Zhang J, Leung GY, Clark RE. Chronic physical conditions in older adults with mental illness and/ or substance use disorders. *Journal of the American Geriatrics Society.* 2011;59(10):1913-1921.

77. Piane GM, Smith TC. Building an evidence base for the co-occurrence of chronic disease and psychiatric distress and impairment. *Preventing Chronic Disease.* 2014;11:E188.

78. Rosen-Reynoso M, Alegria M, Chen CN, Laderman M, Roberts R. The relationship between obesity and psychiatric disorders across ethnic and racial minority groups in the United States. *Eating Behaviors.* 2011;12(1):1-8.

79. Welsh ER, McEnany GP. Approaches to reduce physical comorbidity in individuals diagnosed with mental illness. *Journal of Psychosocial Nursing and Mental health Services.* 2015;53(2):32-37.

80. Adriaansen JJ, van Leeuwen CM, Visser-Meily JM, van den Bos GA, Post MW. Course of social support and relationships between social support and life satisfaction in

spouses of patients with stroke in the chronic phase. *Patient Education and Counseling.* 2011;85(2):e48-52.

81. Hand C, Law M, McColl MA, Hanna S, Elliott S. An examination of social support influences on participation for older adults with chronic health conditions. *Disability and Rehabilitation.* 2014;36(17):1439-1444.

82. Henwood BF, Stanhope V, Brawer R, et al. Addressing chronic disease within supportive housing programs. *Progress in Community Health Partnerships: Research, Education, and Action.* 2013;7(1):67-75.

83. Moreno-Gavino L, Bernabeu-Wittel M, Mendoza-Giraldo D, Sanz-Baena S, Galindo-Ocana FJ. Caregivers' features and social support in patients with advanced medical diseases. *European Journal of Internal Medicine.* 2013;24(6):e72-73.

84. Woods SB, Priest JB, Roush T. The biobehavioral family model: testing social support as an additional exogenous variable. *Family Process.* 2014;53(4):672-685.

85. Jolles EP, Clark AM, Braam B. Getting the message across: opportunities and obstacles in effective communication in hypertension care. *Journal of Hypertension.* 2012;30(8):1500-1510.

86. Salt E, Rowles GD, Reed DB. Patient's perception of quality patient--provider communication. *Orthopedic Nursing.* 2012;31(3):169-176.

87. Keller AO, Gangnon R, Witt WP. The impact of patient-provider communication and language spoken on adequacy of depression treatment for U.S. women. *Health Communication.* 2014;29(7):646-655.

88. Salt E, Rayens MK, Frazier SK. Predictors of perceived higher quality patient-provider communication in patients with rheumatoid arthritis. *Journal of the American Association of Nurse Practitioners.* 2014;26(12):681-688.

89. Sikorskii A, Given CW, Given BA, et al. Do treatment patterns alter beliefs cancer patients hold regarding oral oncolytic agents? *Psycho-Oncology.* 2017;27(3):1005-1012.

90. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2008;11(1):44-47.

91. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. *The Annals of Pharmacotherapy.* 2004;38(9):1369-1376.

CHAPTER TWO: BURDEN OF TREATMENT IN PATIENTS WITH CANCER AND MULTIMORBID CONDITIONS: A CONCEPT ANALYSIS
(Manuscript One)

Introduction

Patients with cancer encounter a number of challenges as they move through their care trajectory. Add one or more other chronic conditions to their cancer, and these challenges are likely to multiply. This distress of being a patient can be characterized as the *burden of treatment*. Burden of treatment (BOT) is the combination of the healthcare tasks required to manage one's disease(s) ("workload"), and the individual's "perspective" of that workload.[1] BOT is a new and evolving concept that has emerged with the increased prevalence of chronic diseases. Due to the increased emphasis placed on self-management of chronic diseases, patients with chronic diseases are being asked to complete more healthcare tasks than ever before.[2-4] The increased responsibility being placed on patients for self-management of their treatment is due in part to a paradigm shift of treatment taking place in the home, rather than the clinic or hosital.[5] This paradigm shift is due in part to financial pressures related to insurance coverage and hospital reimbursement for acute-care hospital beds. BOT is a concept that will prove to be vital in examining the continuing trend of the added workload to patients' cancer and multimorbid treatment regimens and the challenges experienced by patients to manage their cancer and other chronic conditions.

Chronic disease management includes "drug management, self-monitoring, visits to the doctor, laboratory tests, lifestyle changes, and other actions that take place in addition to the other work patients and their caregivers must do as part of life."[6-8] For cancer patients actively receiving treatment, whether infusion in a controlled clinical setting or oral agents in the home, there is much that is needed to be done to manage their treatment regimen, to manage symptoms and side effects, and to coordinate their care. Cancer is a dynamic disease in that the disease status and prognosis change frequently. Because of these frequent status changes, treatment regimens must change with the disease status.[9]

Unlike some chronic diseases, such as diabetes or hypertension, cancer patients are not able to easily check if their treatment is working, such as monitoring blood glucose and blood pressure. This uncertainty of cancer disease status can lead to more distress for patients through an increased workload when treatment regimens often require dose modifications or unplanned rest periods.[10] Changes in disease status and treatment regimens can also bring about a new set of symptoms and side effects, which can have an impact on the distress and quality of life of cancer patients.[9] These changes in distress and quality of life can be positive or negative, depending on the prognosis and amount of work that must be done by the patient to manage the changing cancer disease status.[9]

The addition of another chronic condition to cancer can bring about added tasks and may produce added distress for an individual who is already in a challenging situation with their cancer. Chronic disease management requires a wide variety, and often a large number, of patient tasks. Self-management, which is the behaviors patients engage in order to effectively control their conditions(s),[11] is considered a vital concept when examining how individuals may or may not be successful in controlling their chronic disease(s).[12-14] With the shift from hospital to home, patient self-management has become more important in examining how individuals with chronic disease care for themselves, and what factors may lead to reductions in emergency room (ER) visits and hospitalizations. With cancer patients already under a substantial amount of distress and having a number of tasks to manage, having another chronic disease to manage will likely increase this distress and workload.[15]

Another chronic disease not only brings about mental and physical stress through an increased workload of healthcare tasks, but individuals can also see a financial burden with the addition of a chronic disease.[12,14,16-20] In addition to these factors, which a patient may be able to control, having a multimorbid condition can be associated with interactions between diseases and medications, which patients may be unaware of or have difficulty managing.[4,15,21,22] One chronic condition, especially cancer, is complex enough in itself, but having another multimorbid

condition can have a substantial impact that individuals may not have the knowledge or resources to manage the workload and stress that is associated with multimorbidity.

In the conceptual literature, BOT has been defined as the workload of being a patient."[1,6-8,23,24] The three primary contributors to the conceptualization of burden of treatment, Tran, Sav, and Eton, present their work in different forms, but come to the following similar conclusions: burden of treatment is a multidimensional construct; it is influenced by four primary domains of antecedents (patient, social, disease/treatment, and healthcare system); and as burden of treatment is increased, patient quality of life decreases and poor patient outcomes result.[1,6,24] Each of these three research teams cited the normalization process theory (NPT) as being part of the foundation for the concept of BOT.[1,6,24] NPT is focused on incorporating practices into everyday life and sustaining these practices as part of a routine.[25] This integration of practices can be at an individual or group level. Along with the integration of tasks that need to be completed, NPT incorporates "reflexive monitoring," which is the process of how individuals understand the ways in which these practices affect themselves and those around them.[25] Although NPT incorporates the subjective patient perspective that is involved in BOT, little emphasis is placed on patient perspective of workload within the current BOT literature.[1,6,24]

When examining burden of treatment, it is important to examine the quantity and complexity of the patient's treatment workload, but also the perspective of how that workload may impact the individual. Two individuals with the same number of required tasks may not have equal or similar BOT. Each individual's perspective of their conditions and the required tasks must be considered. A negative perspective or greater distress may impact the individual's ability to complete these tasks, and therefore, to properly manage their conditions. For this reason, it is crucial to describe an individual's treatment workload, and then describe how this workload may being positively, or negatively impact their daily life. Not every patient will have a similar perspective and distress level, even if patients having a similar workload to manage. Therefore, it is important to not only examine a patient's workload, but also the

patient's perspective of their diseases and workload. Examining these perspectives may then provide insight into how an individual is able to manage their workload and chronic conditions.

Purpose

The purpose of this work is to analyze the concept of BOT, specifically within cancer patients with multimorbid conditions, using Rodger's evolutionary concept analysis method.[26,27] This concept analysis will comprehensively examine the attributes, antecedents, and consequences of burden of treatment within cancer patients with multimorbid conditions in order to establish a conceptual model for future research with cancer patients with multimorbid conditions. This analysis will lay a foundation for researchers to understand the healthcare tasks required of this population, as well as patients' perspective of this workload. The hope is that future research teams will develop interventions aimed at reducing BOT in cancer patients and empowering cancer patients with multimorbid conditions to effectively manage their cancer and other chronic conditions.

A concept analysis of burden of treatment within cancer patients with multimorbid conditions fills three gaps within the general concept of burden of treatment, but also fills gaps specifically within this population. First, this work will emphasize the importance of the subjective patient perspective in relation to the workload needed to manage their cancer and multimorbid conditions. Minimal research has been conducted examining the workload and perspective of cancer patients actively receiving treatment while also having to manage other multimorbid conditions.[15] Some work has been done with conditions commonly associated with cancer, such as diabetes or heart disease, but these studies often examine the multimorbid conditions in terms of the outcome variables of interest, such as increased hospitalizations.[15,21,28] However, these previous works have rarely looked at the subjective side of BOT, patient perspective. Second, this work will provide insight not only for researchers, but also clinicians who may struggle to understand the challenges that are faced by their patients actively receiving cancer treatment while also trying to manage their other chronic conditions.

Lastly, this concept analysis will include development of a conceptual model focused on cancer patients with multimorbid conditions in order to inform future research and practice that will help to ease the daily burden of treatment of this population. This conceptual work will help provide a better understanding of BOT, including its attributes, antecedents and consequences, for both researchers and clinicians.

Methods

Rodger's evolutionary concept analysis method was used to complete this concept analysis.[26,27] **Table 2.1.** provides the steps of Rodger's method, as well as the results of this concept analysis for each step. This method was chosen, in part, due to Rodgers calling for a particular realm or sample to be chosen as the focus of the concept. For this work, cancer patients with multimorbid conditions is the sample that fulfills this step of the process. Rodger's process also emphasizes that concepts are dynamic, and that they change over time due to the context in which the concept is examined.[26,27] Burden of treatment is a concept that has the potential to change frequently as the result of a patient's situation. Therefore, Rodger's process is a justified framework to follow in examining BOT.

Table 2.1. Rodger's Evolutionary Concept Analysis Process

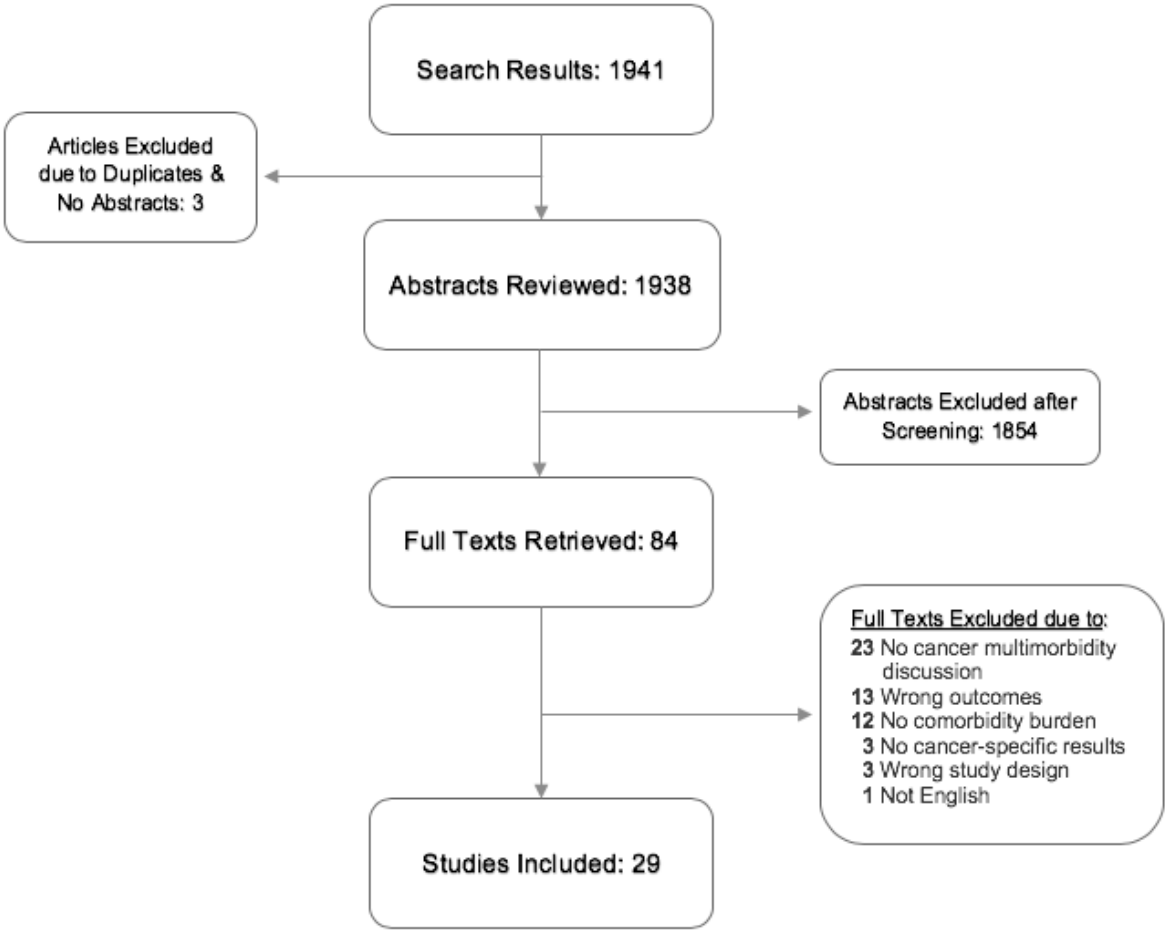
Rodger's Concept Analysis Primary Activities	Concept Analysis Results
1. Identify the concept of interest and associated expressions (surrogate and related terms).	1. Burden of treatment (BOT) – patient workload, patient perspective, distress, cognitive representation of illness
2. Identify and select the setting and sample for data collection.	2. Disciplines: medicine, nursing, psychology, sociology, public health. Databases: PubMed, CINAHL, PsycINFO, Cochrane Abstract time period: 2013-2017
3. Collect data to identify the attributes and contextual basis of the concept including interdisciplinary, sociocultural, and temporal (antecedents and consequences) variations.	3. Review of the literature and data coding conducted for 29 relevant articles.
4. Analyze data regarding the characteristics of the concept.	4. Defining attributes: patient workload and patient perspective. Antecedents: patient, social, disease/treatment, and healthcare system factors. Consequences: adherence/non-adherence; clinical outcomes; treatment modifications; health and well-being.
5. Identify a model case of the concept.	5. A model case was discussed comparing a cancer patient with a cancer patient that has one or more multimorbid conditions.
6. Identify implications and hypotheses for further development of the concept.	6. Individuals with cancer and multimorbid conditions are more likely to experience greater BOT. This work provides a new roadmap to inform future research and practice focused on decreasing the daily struggles within this population.

A systematic search was performed using the following literature databases: PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and the Cochrane Library Database. Combinations of MeSH terms and free text key words, having similar meanings, were utilized during the search process. Keywords for burden of treatment included: burden of treatment, treatment burden, medication burden, disease burden, and illness burden. Keywords for cancer and other conditions included: cancer, chronic condition/disease/illness, comorbidity/comorbid condition, chronic* and multimorbid*. Additional

searches were done using variations of diabetes, cardiovascular disease, and kidney disease. These conditions were used specifically by name due to their frequent association with cancer. All combination search queries were imputed into all four databases.

The eligibility criteria for articles were the following: English language, the sample must be adults 18 years or older, and studies published within the last 5 years. This time period was chosen to be consistent with the use of burden of treatment and to ensure that the included literature was as recent as possible. Only original published research articles were included. Conference abstracts, editorials, and dissertations/theses were excluded. Articles that utilized mortality as the only outcome measure were excluded due to the limited insight this outcome measure contributes to burden of treatment. After eligible articles were identified, each article was coded for attributes, antecedents, consequences, contextual basis, related/surrogate terms, and conceptual/operational definitions. Data were then extracted based on these codes to be included in the corresponding sections of the analysis, in order to fulfill Rodger's process. **Figure 2.1.** shows the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram of the reviewed and included articles. In total, 29 full text articles were included for data extraction within this concept analysis. **Table 2.2.** describes some of the details of each of the included articles.

Figure 2.1. PRISMA Flow Diagram of Reviewed Articles



Components of Concept Analysis

This section provides definition of each of the components of Rodger's concept analysis process, including attributes, antecedents, consequences, contextual basis, related/surrogate terms, conceptual/operational definitions, and a model case.[27] *Attributes* are the components that make up the concept. For burden of treatment, this would be the two primary components, patient treatment workload and the patient perspective of this workload. *Antecedents* are the events or phenomena that precede the concept and may impact the concept. Examples of potential antecedents for burden of treatment include individual's age, marital status, and multimorbid conditions. *Consequences* are the result of the concept occurring or not occurring.

An example could be a clinical outcome, such as a hospitalization, or an individual's quality of life. Consequences can be proximal or distal outcomes and have the potential to impact of be a part of BOT. For example, a treatment modification can be a consequence, but also a component of BOT. When treatment modifications occur as a consequence, the workload and BOT can be altered, as well. *Contextual basis* is the circumstance in which the concept is viewed and who it is viewed from. For burden of treatment, this may be the viewpoint of a patient with cancer and diabetes, or it could be from the viewpoint of a cardiologist caring for a patient with a new diagnosis of cancer.

Surrogate terms are those words that have a similar meaning to that of the concept and may be used to describe the same concept within the literature. For burden of treatment, this may be healthcare tasks. *Conceptual and operational definitions* provide a comprehensive meaning of the concept when examining the concept from a theoretical standpoint, as well as objectively measuring the concept. A conceptual definition is a theoretical or abstract definition of the concept of interest. An operational definition is how researchers measure a specific concept or variable. A *model case* of the concept demonstrates a specific example of the concept being utilized within the specific setting or population being studied.

Results

Attributes

As previous burden of treatment literature has discussed, BOT can be broken down into both objective and subjective components or measurements. For this work, the objective attribute is patient workload, and the subjective attribute is the patient perspective of that workload.

Patient Workload. As exemplified by the standard definition of burden of treatment, "the workload of being a patient," the concept is mostly viewed for the required tasks that individuals must undertake in order to manage their chronic disease(s).[1,6,23,24] These activities vary, depending on the disease population and the individual patient. From the included articles,

patient workload can be further divided into several subcategories: disease and treatment demands, interaction with the healthcare system, and financial responsibilities,

The number of treatment-related tasks can be a substantial burden for individuals with cancer. This burden is further multiplied when cancer patients have additional chronic diseases that require medical management.[15] The most commonly cited medication related contributors to burden of treatment were having to fill prescriptions, complexity or difficulty with taking medications, the total number of medications a patient is required to take for their cancer and other diseases, and managing side effects associated with medication regimens.[29-39] As the number of multimorbid conditions increased, so did the average number of medications that patients were required to take.[30,31,34,37,38,40] Symptoms and side effects were associated with cancer, other chronic conditions, and the medications patients were required to take to manage their cancer and other conditions. The management of symptoms and side effects often included taking more medications for pain, nausea, vomiting, and infection.[31,33,35,39,41] In addition to having to comply with medications and treatments to manage cancer and other conditions, lifestyle changes were discussed as adding to the patient workload. These lifestyle changes included proper dieting, exercise, smoking cessation, decreased alcohol consumption.[30,32,42-46]

Similar to the number of medications, as the number of chronic conditions increased, so did the frequency with which individuals interact with the healthcare system. Studies that evaluated individuals' interactions with the healthcare system did so by calculating the total number of days interacting with the healthcare system, number of providers, and the number of visits to a clinic or hospital.[33,46,47] While the number of medications and the amount of time an individual spends interacting with the healthcare system increases, the financial burden for these individuals typically increases as well.[33,37,40,43,48-50] Treatment and medications, hospital and ER visits, and physician appointments were cited as contributing the greatest burden of treatment.[33,40,43,48,49] Financial concerns for individuals were more burdensome for those with an increased number of multimorbid conditions.[44,49] The increased number of conditions and

treatment require patients to manage an increased financial responsibility, either by making sure their insurance covers the cost or having to pay out of pocket. Financial concerns were related both to worrying about maintaining employment to have insurance coverage, paying for insurance, and out of pocket (OOP) costs.[33,40,43]

Patient Perspective. The patient perspective is how the individual perceives their disease(s) and the tasks needed to manage their illnesses (workload). Only three studies included a focus on the subjective nature of burden of treatment than the patient workload components.[39,41,43] The studies that did include insights into individual's perspective focused on how their disease and symptoms impacted their daily life and ability to manage their conditions, individual's ability to cope with their conditions and the tasks brought on by them, and patient's perception of their communication and relationship with providers.[39,41,43] One study examined how much symptoms bothered patients, and how the number of multimorbidities relates to the symptom severity and how bothersome symptoms are.[39] They found a correlation between an increased number of severe symptoms and an increase in number of multimorbid conditions. Additionally, individuals with more multimorbid conditions felt bothered more by their conditions. The odds of feeling bothered by a multimorbidity increased as the number of severe symptoms increased.[39]

The only qualitative study included found that individual's stress was primarily focused around five themes: lack of family support, communication barriers with the healthcare system, stress related to be a minority (i.e. racial, gender, or socioeconomic status), caregiver burden, and lack of spiritual support.[43] Having to manage one or more chronic conditions brought on added stress and burden to the individuals included within the study. These stressors made it difficult to manage their conditions and daily lives. When asked how they might be able to cope with these stressors, individuals identified that access to certain resources, being knowledgeable about their diseases and treatment, and having family and support were the best ways to cope with the burden. Related to barriers to communication with healthcare providers, the final study that included patient perspective examined patient-provider communication by

having patients rate their perceived communication with providers.[41] They found that cancer patients with depression and hopelessness had significantly worse perceived communication with their providers. They also pointed out that when patients perceive their communication with providers as poor, this can lead to greater psychological distress for patients with cancer.

Antecedents

The antecedents included in this concept analysis are placed in four subcategories: patient, social, healthcare system, and disease/treatment. As defined earlier, some or all of the antecedents must occur before the concept of interest (i.e. BOT) can occur.

Patient Characteristics. Several patient characteristics were noted as being associated with an increased burden of treatment. Additionally, certain patent characteristics were associated with individuals that had increased numbers of multimorbid conditions and experienced negative consequences within the included studies. Females and older adults typically experienced an increased burden of treatment.[29-32,43,48,51] Older adults were more likely to have a greater number of multimorbid conditions, and therefore have a greater workload than younger adults. Additionally, socioeconomic status (SES), race, location of living, and education status played a role in the level of burden that patients experienced in some studies.[32,35,43,45] This increased burden is due in part to the difficulties in access to care of lower SES status, limited insurance coverage, and individuals' proximity to medical facilities.[32,35,43,45]

Social Factors. Having a close support system was associated with a lower burden of treatment for cancer patients with multimorbid conditions.[30,33,35,38,50] These supports systems typically consisted of a spouse, family members, or close friends.[30,33,35,38,50] A support system can help to alleviate some of the workload patients need to complete in order to manage their cancer and other conditions. Although having a support system was often associated with a lower BOT, some individuals felt they were causing more stress for their support system by having them help with daily tasks. These individuals felt that they were a burden to their caregiver or others

helping them, which may negatively affect both the patient and those within the support system.[43]

Disease/Treatment Factors. Disease and treatment factors were often noted as the greatest contributors to patients' overall burden of treatment. For cancer, the factors most greatly contributing to BOT were site of cancer, stage, and prognosis. Later stage cancers with poor prognoses were associated with greater burden of treatment.[29,30,38,49,52,53] For multimorbid conditions, certain conditions contributed to an increased burden, including diabetes and kidney disease, but the overall number of conditions appeared to have a greater impact on burden of treatment.[30,38,45-47,49-56] As the number of conditions increased, so did the workload,[30,38,45-47,49-56] and often a worsening perspective on one's overall BOT.[39,41,43] Additionally, psychological multimorbid conditions, such as depression, anxiety, and post-traumatic stress disorder (PTSD), were associated with a greater BOT.[35,36,38,41,43] While these psychological conditions can increase one's workload with appointments with therapists, medications, and other tasks to manage the disease, these conditions can also make it difficult for an individual to cope with the stress of having to manage cancer and other conditions.[35,38,41,43]

Healthcare System Factors. Healthcare system factors are those variables that involve the patient to interact with the healthcare system in any way, whether that be hospital stays, ER visits, physician appointments, or insurance companies. The size of a hospital, teaching versus non-teaching hospitals, and urban versus rural hospitals had an impact on the level of burden and certain outcomes for patients.[48,57] Individuals being treated at higher patient volume, urban, and teaching hospitals were associated with worse outcomes.[48] Patients' access to and type of insurance played a role in the level of BOT that patients experienced. As would be expected, insurance was closely related to financial burden that patients faced, in terms of being able to fulfill certain prescriptions and the OOP costs that were associated with treatment and medications.[38,43,48-50,55,57] Another aspect of the healthcare system that impacted patients' BOT, particularly their perspective of their situation, was their relationships with providers.[41,43] Patients

may not feel that their voices are being heard by providers, or that they have received enough information regarding medications or treatment.[41,43] A strained relationship with providers may lead to poor outcomes for individuals.[41,43] BOT may be positively, or negatively, impacted by some combination of patient, social, disease/treatment, and healthcare system antecedent factors. These factors must occur before BOT can happen, and as they change so will the patient workload and perspective.

Consequences

This work identified several outcomes and consequences within the included studies. The outcome of some studies was determined to be patient workload, which is an attribute of BOT, while other outcomes were identified as a consequence of BOT occurring. These consequences were grouped into four categories: adherence/non-adherence, clinical outcomes, treatment modifications, and health and well-being.

Adherence/Non-adherence. Adherence, or compliance to a medication or treatment regimen, is a commonly evaluated outcome for studies including individuals taking medications for chronic conditions.[58] More multimorbid conditions and a greater number of medications to manage were associated with greater non-adherence among individuals with cancer who had other conditions.[30,40] Not only can an increased workload lead to greater non-adherence, but financial burden may impact an individual's ability to adhere to their treatment regimen.[40] Not being able to fill prescriptions or having difficulty paying for prescriptions at the proper time can negatively impact an individual's treatment regimen.[33,40,49] Not only is adherence a concern for medications, but also lifestyle changes, which are vital to many chronic conditions. For individuals with both cancer and heart failure, non-adherence to body weight control, reduced sodium intake, fluid restriction, and smoking cessation led to poor outcomes.[30]

Clinical Outcomes. Clinical outcomes in the included articles covered a wide range of consequences, including hospitalizations, readmissions, ER visits, advanced progression in disease status, surgical complications, and other adverse events, such as venous

thromboembolism (VTE). The majority of included articles that examined clinical outcome consequences found that cancer patients with more multimorbid conditions experienced higher rates and more severe outcomes than cancer patients with no multimorbid conditions.[31,37,45-48,52-54] Specific to advanced cancer disease status, individuals with cancer and diabetes had significantly larger tumor masses than those with cancer alone, according to two studies.[42,44] Post-surgical complications and 30-day readmission rates were higher in individuals with multimorbid conditions than cancer alone.[46,54] Systemic infections, VTEs, anemia, and skeletal events were more likely to occur with multimorbid conditions, especially when having 3+ conditions in addition to their cancer.[37,45,48,52,53] In general, individuals with more multimorbid conditions experienced a greater symptom burden than those with cancer alone.[31,33,35,39,41]

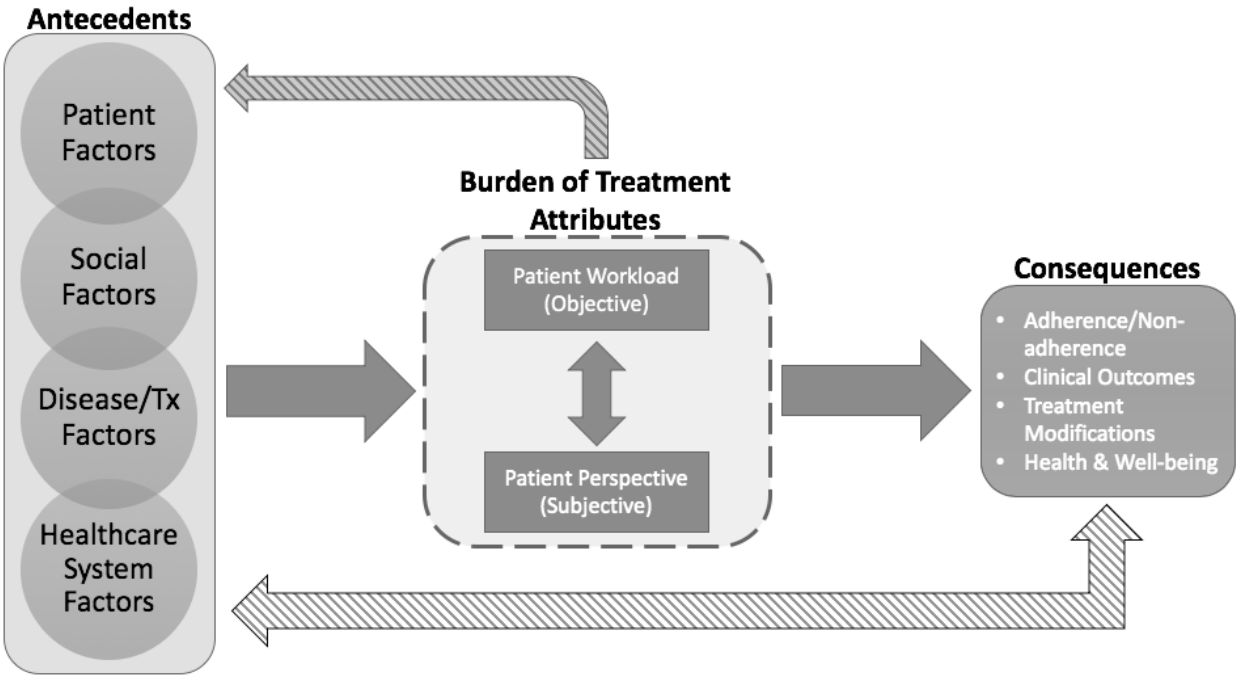
Treatment Modifications. Treatment decisions and modifications were common outcome variables for several included studies, especially comparing medication regimen modifications and treatment plan decisions between individuals with cancer only and those with cancer and other multimorbid conditions.[29,31,32,34,43,54,57] Treatment modifications were most often the result of symptom/side effect profiles, current treatment not working, or a change in an individual's disease status. Cancer patients with multimorbid conditions experienced increased rates of symptoms and side effects, which led to more treatment modifications.[34,54] Additionally, individuals with cancer and multimorbid conditions experienced higher rates of poor clinical outcomes, or adverse events, which also led to higher rates in treatment modifications.[34,54] While higher rates of treatment modifications for individuals with cancer and multimorbid conditions can contribute to a higher burden of treatment, there were instances noted of treatment decisions with these individuals that led to a lower workload.[34,54] Two studies found that individuals with cancer and multimorbid conditions were less likely to receive certain treatments, primarily surgeries, due to having increased risk factors related to their multimorbid conditions.[32,57] This may decrease the patient workload, but it has the potential to negatively impact one's perspective, if the patient believes they are not receiving the best treatment.

Health and Well-being. The final category of consequences primarily focuses on the general health of an individual. The included studies evaluated health and well-being with a multitude of variables, including quality of life (QOL), health-related quality of life (HRQOL), physical functioning, performance status, general health status, and productivity.[30,34,35,41,50,51,55] Overall health status and quality of life became worse as the number of multimorbid conditions increased. Productivity and employment decreased for individuals with cancer and multimorbid conditions.[50,51,55] These individuals were forced to take more sick leave time and disability pay than individuals with cancer alone.[55] Whether one views symptoms and side effects as a part of clinical outcomes or health and well-being, symptoms have a substantial impact on the QOL of individuals. Individuals with cancer and multimorbid conditions more often experienced a greater symptom burden, and therefore worse QOL, than individuals with cancer alone.[31,50,51]

Burden of Treatment Morbidity (BOTM) Model

The BOTM Model, developed as part of this dissertation, focuses on the relationships among the antecedents, attributes, and consequences of BOT. Much like a mediation model, there is a direct relationship between the antecedents and consequences, with the attributes of BOT serving as the mediator and therefore helping to explain the relationship between the antecedents and consequences. Unlike a traditional mediation model, the BOTM model shows feedback loops from from both the attributes and consequences back to the antecedents. The feedback loops illustrate that when certain attributes change or a consequence occurs, there is potential for impact on some antecedents. Including both the mediation impact of the attribute and the feedback loops emphasizes the BOT as a dynamic process. The BOTM model allows researchers and clinicians to include antecedents, attributes and consequences that are specific to their work in order to answer new research questions or influence new practice changes.

Figure 2.2. Burden of Treatment Morbidity (BOTM) Model



Discussion

As individuals with cancer continue to live longer, the percentage of individuals with cancer and one or more multimorbid conditions will continue to increase. Having to manage multiple conditions, especially one as burdensome as cancer, can be a difficult challenge for many individuals. For this reason, there is a great need for the examination of the concept of burden of treatment within this population. Utilizing the conceptual model and operational definition is imperative not only to understand the burden and daily challenges faced by individuals with cancer and multimorbid conditions, but also to begin to develop interventions to prevent or decrease that burden. This concept analysis is the first to examine the concept of burden of treatment specifically within individuals with cancer and multimorbid conditions.

Much like other works that are focused on burden of treatment, this concept analysis discussed the dynamic nature of BOT, no matter which chronic conditions an individual has to manage. Burden of treatment is impacted by a number of factors, and therefore the attributes of

patient workload and perspective have the potential to change often. Some of the antecedent factors minimally change, such as age, sex, race, marital status, and SES. While other antecedent factors have the potential to change more often, such as certain disease and treatment factors. Even if antecedent factors are remaining the same, the attributes of burden of treatment have the potential to change frequently. If a new medication is added to a treatment regimen for a cancer patient, this can impact interactions with medications prescribed for multimorbid conditions, how often patients must interact with their oncology team, the ability for the patient manage their cancer and other symptoms, or the perspective of the individual. There are many factors that can shift each for these patients. Although complex and difficult to evaluate, burden of treatment is a necessary concept to examine for individuals with cancer and mulitmorbid conditions. Utilizing the concept of BOT allows researchers and clinicians to evaluate the daily challenges faced by this population.

Model Case. For example, take a model case of an older adult male with prostate cancer, diabetes, and hypertension. This individual is required to take medications for all three conditions, including intravenous (IV) chemotherapy. His latest tumor markers show disease progression and that the IV chemotherapy is proving to be ineffective. For this reason, his oncologist changes his treatment regimen to an oral anticancer agent that is accompanied by an oral glucocorticoid. With this change in disease status and treatment regimen, this individual now has a new workload, added stress, and possible negative emotions related to this news. Additionally, he is not aware that the newly prescribed glucocorticoid may cause increased blood glucose levels, which will require him to adapt how his diabetes is managed. After taking the glucocorticoid for more than a week, the patient has been noticing his blood glucose levels rising. Upon a visit to his PCP, the patient is frustrated to learn that he was not informed by his oncology team that the newly-prescribed medication has the potential to cause increased blood sugar levels. While still not providing a full picture, this brief example touches on the complexities and challenges faced by an individual with cancer and other multimorbid

conditions. As one aspect of his treatment changes, so do several other aspects of his life and management of other diseases. Additionally, this example discusses the patient perspective that can change as an individual's workload changes.

As the example illustrates, there a number of factors, both preceding burden of treatment (antecedents) and components of BOT, that researchers and clinicians need to focus on to better address the challenges faced by individuals with cancer and multimorbid conditions. For antecedents, this concept analysis showed that individuals of older age, female sex, SES, minority races, lacking a social support system, have advanced cancer, and a greater number of multimorbid conditions are faced with a greater overall burden of treatment. This patient workload may be a greater number of medications to manage, complex treatment regimens, financial burden, increased interactions with the healthcare system, or having to manage lifestyle changes. The number of tasks and difficulty in managing them is unique to each individual, and therefore each person has a different perspective of the workload required of them to manage their conditions. Both the workload and a patient's perspective have the potential to change as antecedents and other events occur. Unfortunately, there were only a small number of included studies that had some focus on the subjective nature of burden of treatment, which displays a gap in the evidence of patient perspective of cancer patients with multimorbid conditions. This concept analysis also depicted that the antecedent factors and attributes of burden of treatment have an impact on consequences or outcomes. Those with more multimorbid conditions generally experience poorer adherence,[30,40] more treatment regimen modification,[29,54] worse clinical outcomes,[45,46,52] and poorer overall health than those with cancer alone.[33-35]

The results of this conceptual analysis provide a number of research and practice implications. Antecedent factors have been identified that researchers and clinicians can target to prevent of reduce the burden of treatment and poor outcomes. This work developed a conceptual model focused on burden of treatment within the population of individuals with

cancer and multimorbid conditions. This concept analysis provides specific categories and variables for researchers to include in their work, as well as a visual representation of the relationship of antecedent factors, burden of treatment attributes, and consequences. This is not to say that all variables discussed within this work should be included within one study. Researchers should understand their population of interest and research aims and use this conceptual model as a guideline to inform their work. Similar to its implications for researchers, this work can help clinicians, whether oncology focused or with expertise in other conditions, educate and communicate to patients the importance of certain aspects of burden of treatment. Oncologists may also need to alter treatment plans in order to reduce adverse outcomes that may result in patients managing their cancer and other conditions. This work also points out the vulnerable populations (e.g. older adults, low SES, etc.) that clinicians may need to focus on more than others.

Limitations

Much like any systematic search, this concept analysis is not without its limitations. The five-year time period from 2013-2017 was chosen to include the most current literature, while also limiting the number of articles to be reviewed. Although this concept analysis included a substantial number of articles, having only a five-year time period for inclusion may have excluded potential useful studies. Although a few multimorbid conditions that are often associated with cancer were specifically included in the search terms, not all conditions were searched for by name. This may have limited the studies that resulted from the databases. This author decided to excluded articles that only included mortality/survival as an outcome measure. The inclusion of these studies may have provided evidence for the impact of cancer and multimorbid conditions on long-term survival, but this author felt that it did not add a great deal in terms of insight to patients' burden of treatment. The final limitation is the decision to not include studies that focused only on caregivers of individuals with cancer and multimorbid conditions. While including these studies would have provided insight to the social support

network and workload of patients, the studies did not directly collect data from patients themselves and were therefore excluded.

Conclusions

This concept analysis and conceptual model are aimed at examining the concept of burden of treatment within the population of individuals with cancer and multimorbid conditions. This work identified that there are a number of factors that must take place before BOT can occur, and that these antecedent factors can have a direct relationship with certain consequences, as well as BOT having an impact on that direct relationship. BOT is a complex, dynamic concept that can be challenging for researchers to conceptualize, and even more so operationalize. Without a strong body of literature, clinicians have a difficult time utilizing BOT and the associated variables and outcomes within their practice. This work provides a much-needed conceptualization and model for researchers focused on the daily challenges of individuals with cancer and multimorbid conditions to better inform research questions and study designs. The hope is for this work to lay a conceptual foundation for a program of research that is aimed at minimizing the daily burden of treatment faced by this population, as well as to influence other researchers to do the same. The goal is to guide future research to answer questions and develop interventions to accomplish this goal, so that clinicians are able to have informed conversations with patients who struggle to manage both their cancer and multimorbid conditions.

Table 2.2. Study Details for Included Articles (n=29)

Study (Publication Date)	Country	Study Design	Participants	Multimorbid Conditions
Bayliss et al. (2013)	USA	Retrospective cohort	539 cancer patients	Cardiovascular, hyperlipidemia
Chaudhary et al. (2013)	India	Prospective cohort	358 operable cancer patients	Cardiovascular, hypertension, diabetes, etc.
Dowling et al. (2013)	USA	Retrospective cohort	4,960 cancer survivors, 64,431 non-cancer	Cardiovascular, diabetes, and MEPS priority conditions
Fotos et al. (2013)	Greece	Retrospective cohort	199 heart failure patients	Hypertension, CKD, chronic respiratory failure, cancer, mental illness
Khorana et al. (2013)	USA	Retrospective cohort	17,284 cancer patients, 17,284 non-cancer	Charlson Comorbidity Index
McLean et al. (2013)	Ireland	Retrospective cohort	52 palliative care cancer patients	Hypertension, cardiovascular, diabetes, dyslipidemia, COPD, depression, arthritis
Antczak et al. (2014)	Canada	Retrospective cohort	144,889 RCC with bone metastasis	Charlson Comorbidity Index
Hart et al. (2014)	USA	Retrospective cohort	488 pancreatic cancer	Diabetes
Islam et al. (2014)	Australia	Cross-sectional survey	4,574 older adults	Cancer, hypertension, chronic respiratory, depression, diabetes, stroke, cardiovascular
Kayser et al. (2014)	USA	Qualitative focus groups	Chronic disease patients, caregivers, and healthcare professionals	Cancer, cardiovascular, HIV/AIDS
Sarfati et al. (2014)	New Zealand	Retrospective cohort	524 cancer patients	C3 comorbidity index
Baz et al. (2015)	USA	Semi-structure qualitative interviews	20 multiple myeloma patients	Not-specified
Gershon et al. (2015)	Canada	Retrospective cohort	7,241,591 COPD patients	Cancer, cardiovascular, diabetes, musculoskeletal, mental illness
Gilmelius et al. (2015)	Sweden	Retrospective cohort	1,989 HL patients, 7956 non-cancer	Cardiovascular diseases
Ording et al. (2015)	Denmark	Retrospective cohort	44,035 prostate cancer, 213,810 non-cancer	Charlson Comorbidity Index
Østgård et al. (2015)	Denmark	Retrospective cohort	2792 AML patients	Charlson Comorbidity Index
Thekdi et al. (2015)	USA	Baseline data from RCT	287 RCC patients	Depression, PTSD
Blondeaux et al. (2016)	Italy	Cross-sectional	200 breast cancer treated with AIs, 200 non-cancer	Cardiovascular, diabetes, hypertension
Gheihman et al. (2016)	Canada	Cross-sectional	341 acute leukemia patients	Depression
Guddati et al. (2016)	USA	Retrospective cohort	49,515 metastatic cancer	Cardiovascular diseases
Huang et al. (2016)	USA	Retrospective cohort	78,338 breast cancer	Diabetes, cardiovascular, hypertension, obesity
Jim et al. (2016)	USA	Cross-sectional	1,869 HCT-recipients	Depression
Kleeff et al. (2016)	UK	Retrospective cohort	1,105 pancreatic cancer	Diabetes

Table 2.2. (cont'd)

Study (Publication Date)	Country	Study Design	Participants	Multimorbid Conditions
Maeda et al. (2016)	Japan	Retrospective cohort	152 breast cancer	Diabetes
Neugut et al. (2016)	USA	Retrospective cohort	21,255 breast cancer	Charlson Comorbidity Index
Presley et al. (2016)	USA	Retrospective cohort	7,955 NSCLC	Quantified from ICD-9
Guy et al. (2017)	USA	Retrospective cohort	10,293 cancer survivors, 135,151 non-cancer	MEPS priority conditions
Hawkins et al. (2017)	USA	Retrospective cohort	3,184 cancer survivors, 44,997 non-cancer	Cardiovascular, hypertension, stroke, diabetes, arthritis
Ritchie et al. (2017)	USA	Secondary analysis	3,016 cancer patients	Derived based on chronic condition medications using RxRisk

Abbreviations: MEPS, Medical Expenditure Panel Survey; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; RCC, renal cell carcinoma; C3, Cancer, Care and Comorbidity; HL, Hodgkin's lymphoma; AML, acute myeloid leukemia; PTSD, post-traumatic stress disorder; HCT, hematopoietic cell transplant; ICD, International Statistical Classification of Diseases and Related Health Problems

REFERENCES

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1. Sav A, King MA, Whitty JA, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. *Health expectations : an international journal of public participation in health care and health policy.* 2013;18(3):312-324.

2. Thakkar J, Kurup R, Laba TL, et al. Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. *JAMA internal medicine.* 2016;176(3):340-349.

3. Portz JD, Kutner JS, Blatchford PJ, Ritchie CS. High Symptom Burden and Low Functional Status in the Setting of Multimorbidity. *Journal of the American Geriatrics Society.* 2017;65(10):2285-2289.

4. Pefoyo AJ, Bronskill SE, Gruneir A, et al. The increasing burden and complexity of multimorbidity. *BMC public health.* 2015;15(415).

5. Schoonover H, Corbett CF, Weeks DL, Willson MN, Setter SM. Predicting potential postdischarge adverse drug events and 30-day unplanned hospital readmissions from medication regimen complexity. *Journal of patient safety.* 2014;10(4):186-191.

6. Tran VT, Barnes C, Montori VM, Falissard B, Ravaud P. Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions. *BMC Med.* 2015;13115.

7. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med.* 2014;12:109.

8. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC Med.* 2012;10:68.

9. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK. Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review. *JAMA oncology.* 201 2018;4(1):105-117.

10. Prasad V, Massey PR, Fojo T. Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. *Journal of clinical oncology : Official Journal of the American Society of Clinical Oncology.* 2014;32(15):1620-1629.

11. Miller WR, Lasiter S, Bartlett Ellis R, Buelow JM. Chronic disease self-management: a hybrid concept analysis. *Nurs Outlook.* 2015;63(2):154-161.

12. Ambrosio L, Senosiain Garcia JM, Riverol Fernandez M, et al. Living with chronic illness in adults: a concept analysis. *Journal of clinical nursing.* 2015;24(17-18):2357-2367.

13. McGowan PT. Self-management education and support in chronic disease management. *Primary care.* 2012;39(2):307-325.

14. Bayliss EA, Ellis JL, Steiner JF. Barriers to self-management and quality-of-life outcomes in seniors with multimorbidities. *Annals of family medicine.* 2007;5(5):395-402.

15. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin.* 2016;66(4):337-350.

16. Bayliss EA, Ellis JL, Steiner JF. Seniors' self-reported multimorbidity captured biopsychosocial factors not incorporated into two other data-based morbidity measures. *Journal of clinical epidemiology.* 2009;62(5):550-557.e551.

17. Bayliss EA, Bonds DE, Boyd CM, et al. Understanding the context of health for persons with multiple chronic conditions: moving from what is the matter to what matters. *Annals of family medicine.* 2014;12(3):260-269.

18. Bayliss EA, Bosworth HB, Noel PH, Wolff JL, Damush TM, McIver L. Supporting self-management for patients with complex medical needs: recommendations of a working group. *Chronic illness.* 2007;3(2):167-175.

19. Allen L, Thorpe K, Joski P. The Effect of Obesity and Chronic Conditions on Medicare Spending, 1987-2011. *PharmacoEconomics.* 2015;33(7):691-697.

20. Banerjee D, Perry M, Tran D, Arafat R. Self-reported health, functional status and chronic disease in community dwelling older adults: untangling the role of demographics. *Journal of community health.* 2010;35(2):135-141.

21. Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. *Journal of geriatric oncology.* 2016;7(4):249-257.

22. Ritchie CS, Kvale E, Fisch MJ. Multimorbidity: an issue of growing importance for oncologists. *Journal of oncology practice / American Society of Clinical Oncology.* 2011;7(6):371-374.

23. Eton DT, Elraiyah TA, Yost KJ, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. *Patient related outcome measures.* 2013;4:7-20.

24. Eton DT, Ridgeway JL, Egginton JS, et al. Finalizing a measurement framework for the burden of treatment in complex patients with chronic conditions. *Patient related outcome measures.* 2015;6:117-126.

25. May C, Finch T. Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory. *Sociology.* 2009;43(3):535-554.

26. Tofthagen R, Fagerstrom LM. Rodgers' evolutionary concept analysis--a valid method for developing knowledge in nursing science. *Scandinavian journal of caring sciences.* 2010;24 Suppl 1:21-31.

27. Rodgers BL. *Concept development in nursing: Foundations, techniques, and applications.* 2nd ed. Philadelphia, PA: Saunders; 2000.

28. Spoelstra SL, Given CW, Sikorskii A, Majumder A, Schueller M, Given BA. Treatment With Oral Anticancer Agents: Symptom Severity and Attribution, and Interference With Comorbidity Management. *Oncology nursing forum.* 2015;42(1):80-88.

29. Bayliss EA, Bronsert MR, Reifler LM, et al. Statin prescribing patterns in a cohort of cancer patients with poor prognosis. *Journal of palliative medicine.* 2013;16(4):412-418.

30. Fotos NV, Giakoumidakis K, Kollia Z, et al. Health-related quality of life of patients with severe heart failure. A cross-sectional multicentre study. *Scandinavian journal of caring sciences.* 2013;27(3):686-694.

31. McLean S, Sheehy-Skeffington B, O'Leary N, O'Gorman A. Pharmacological management of co-morbid conditions at the end of life: is less more? *Irish journal of medical science.* 2013;182(1):107-112.

32. Sarfati D, Gurney J, Stanley J, Koea J. A retrospective cohort study of patients with stomach and liver cancers: the impact of comorbidity and ethnicity on cancer care and outcomes. *BMC cancer.* 2014;14:821.

33. Baz R, Lin HM, Hui AM, et al. Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on health-related quality of life. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2015;23(9):2789-2797.

34. Østgård LS, Nørgaard JM, Sengeløv H, et al. Comorbidity and performance status in acute myeloid leukemia patients: a nation-wide population-based cohort study. *Leukemia.* 2015;29(3):548-555.

35. Thekdi SM, Milbury K, Spelman A, et al. Posttraumatic stress and depressive symptoms in renal cell carcinoma: Association with quality of life and utility of single-item distress screening. *Psycho-oncology.* 2015;24(11):1477-1484.

36. Jim HSL, Sutton SK, Jacobsen PB, Martin PJ, Flowers ME, Lee SJ. Risk factors for depression and fatigue among survivors of hematopoietic cell transplantation. *Cancer.* 2016;122(8):1290-1297.

37. Maeda T, Babazono A, Nishi T, Miyazaki H, Tamaki K, Fujii M. The effect of diabetes with pharmacotherapy for breast cancer on care resource use. *Journal of cancer research and therapeutics.* 2016;12(2):876-880.

38. Hawkins NA, Soman A, Buchanan Lunsford N, Leadbetter S, Rodriguez JL. Use of Medications for Treating Anxiety and Depression in Cancer Survivors in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(1):78-85.

39. Ritchie CS, Zhao F, Patel K, et al. Association between patients' perception of the comorbidity burden and symptoms in outpatients with common solid tumors. *Cancer.* 2017;123(19):3835-3842.

40. Neugut AI, Zhong X, Wright JD, Accordino M, Yang J, Hershman DL. Nonadherence to Medications for Chronic Conditions and Nonadherence to Adjuvant Hormonal Therapy in Women With Breast Cancer. *JAMA oncology.* 2016;2(10):1326-1332.

41. Gheihman G, Zimmermann C, Deckert A, et al. Depression and hopelessness in patients with acute leukemia: the psychological impact of an acute and life-threatening disorder. *Psycho-oncology.* 2016;25(8):979-989.

42. Kleeff J, Costello E, Jackson R, et al. The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. *British journal of cancer.* 2016;115(7):887-894.

43. Kayser K, DeMarco RF, Stokes C, DeSanto-Madeya S, Higgins PC. Delivering palliative care to patients and caregivers in inner-city communities: challenges and opportunities. *Palliative & supportive care.* 2014;12(5):369-378.

44. Hart PA, Law RJ, Frank RD, et al. Impact of diabetes mellitus on clinical outcomes in patients undergoing surgical resection for pancreatic cancer: a retrospective, cohort study. *The American journal of gastroenterology.* 2014;109(9):1484-1492.

45. Gershon AS, Mecredy GC, Guan J, Victor JC, Goldstein R, To T. Quantifying comorbidity in individuals with COPD: a population study. *The European respiratory journal.* 2015;45(1):51-59.

46. Huang BZ, Camp MS. Burden of preoperative cardiovascular disease risk factors on breast cancer surgery outcomes. *Journal of surgical oncology.* 2016;114(2):144-149.

47. Presley CJ, Soulos PR, Tinetti M, Montori VM, Yu JB, Gross CP. Treatment Burden of Medicare Beneficiaries With Stage I Non–Small-Cell Lung Cancer. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2016;13(2):398-e107.

48. Antczak C, Trinh VQ, Sood A, et al. The health care burden of skeletal related events in patients with renal cell carcinoma and bone metastasis. *The Journal of urology.* 2014;191(6):1678-1684.

49. Islam MM, Yen L, Valderas JM, McRae IS. Out-of-pocket expenditure by Australian seniors with chronic disease: the effect of specific diseases and morbidity clusters. *BMC public health.* 2014;14:1008.

50. Guy GP, Yabroff KR, Ekwueme DU, Rim SH, Li R, Richardson LC. Economic Burden of Chronic Conditions Among Survivors of Cancer in the United States. *Journal of clinical oncology : Official Journal of the American Society of Clinical Oncology.* 2017;35(18):2053-2061.

51. Dowling EC, Chawla N, Forsythe LP, et al. Lost productivity and burden of illness in cancer survivors with and without other chronic conditions. *Cancer.* 2013;119(18):3393-3401.

52. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer.* 2013;119(3):648-655.

53. Ording AG, Horváth-Puhó E, Lash TL, et al. Prostate cancer, comorbidity, and the risk of venous thromboembolism: A cohort study of 44,035 Danish prostate cancer patients, 1995-2011. *Cancer.* 2015;121(20):3692-3699.

54. Chaudhary RK, Bhaduri D, Bhatia M, Hatti S, Ba R, Meva J. Influence of comorbidity in cancer surgery on treatment decisions, postoperative course and oncological outcome. *Asia-Pacific journal of clinical oncology.* 2013;9(1):47-52.

55. Glimelius I, Ekberg S, Linderoth J, et al. Sick leave and disability pension in Hodgkin lymphoma survivors by stage, treatment, and follow-up time—A population-based comparative study. *Journal of Cancer Survivorship.* 2015;9(4):599-609.

56. Blondeaux E, Musio D, Bruzzi P, et al. Treatment with aromatase inhibitors and markers of cardiovascular disease. *Breast Cancer Research and Treatment.* 2016;160(2):261-267.

57. Guddati AK, Joy PS, Kumar G. Analysis of outcomes of percutaneous coronary intervention in metastatic cancer patients with acute coronary syndrome over a 10-year period. *Journal of Cancer Research and Clinical Oncology.* 2016;142(2):471-479.

58. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2008;11(1):44-47.

CHAPTER THREE: HEALTHCARE SYSTEM CHALLENGES IN PATIENT ACQUISITION OF ORAL ONCOLYTIC AGENTS
(Manuscript Two)

Introduction

A paradigm shift in cancer treatment has led to patients being more responsible for the management of their cancer care.[1-5] The continued upward trend of oral oncolytic agent (OOA) prescriptions means patients are being given intravenous (IV) chemotherapy in a controlled clinical setting less frequently and take chemotherapy orally in the home instead. Although OOAs provide a new convenience for patients, different challenges arise with an OOA prescription, including symptom and medication management.[6,7] A major challenge in a new OOA prescription is getting the OOA into the patient's hands, or patient prescription acquisition. Unlike patients going into a clinical setting to receive IV chemotherapy, patients must either receive OOA prescriptions through the mail or from a specialty or hospital pharmacy. The process of patients acquiring OOAs involves a number of steps that could prevent acquisition of oral agents in a timely manner. This process includes provider prescription, insurance authorization, completion of financial assistance, pharmacy fulfillment, and delivery of OOAs to the patient home.[8] Cancer patients prescribed OOAs are at a critical point in their care trajectory, as most patients have late-stage solid tumors and have received multiple lines of treated prior to being prescribed OOAs.[9,10] For this reason, it is imperative that patients receive their OOAs promptly following a provider's prescription.[11] However, patients face numerous challenges to prompt receipt of their oral agents.

Financial barriers continue to be one of the most common issues that patients face in acquiring their OOAs in a timely manner.[7] The patients' primary insurance must seek insurance approval first, followed by any secondary insurances. At this point, cancer patients still may not be able to afford the copays after insurance coverage, if the OOAs are covered at all.[8,12,13] Oral oncolytic agents are billed to insurance differently than IV chemotherapy because they are considered a prescription medication and not part of a clinic or hospital visit as is the case with

IV. Thus, for many insurances, OOAs are billed within pharmacy benefits, which may result in greater out-of-pocket (OOP) costs than IV chemotherapy with medical treatment coverage. Some insurance companies are not covering full OOA prescriptions, or even the majority of the cost, due to rising costs and a lack of evidence of consistent effectiveness, especially with oral agents only recently approved by the FDA.[14,15] Because of this, patients may need to turn to financial assistance programs through their care system or the drug company that sells the OOA.[8,13] These programs may only be a temporary fix for patients to afford and acquire their OOAs. Going through the process of insurance approval and seeking financial assistance can range from a couple days up to multiple weeks.[8,11,13,16]

Once the medication is approved by insurance, or financial assistance is arranged, obtaining an OOA prescription is not as simple as having it filled at the local drug store. Oral oncolytic agent prescriptions are typically filled through a hospital or institution pharmacy or through a specialty mail-order pharmacy.[8] Specialty pharmacies may experience some delays because they need specific approvals from both prescribers and insurance providers for specific medication, in addition to the wait time for the medication to be shipped to the patient's home with the possibility of shipping delays.[17] When an OOA is prescribed to cancer patients at a vulnerable state, treatment delays can be problematic for their quality of life, as well as for the overall disease prognosis.

Once patients are able to acquire their initial OOA prescription through this occasionally complex process of navigating financing programs and multiple healthcare system personnel, barriers may still arise acquiring subsequent refills.[8] Oral oncolytic agent protocols often involve dose reductions, treatment delays, and medication or treatment changes, which may increase the chance of prescription errors, either by the prescriber or the pharmacy filling the prescription.[12] If a patient is receiving regular shipments of their OOA from a specialty pharmacy (i.e., on schedule with the original treatment protocol timeline), the pharmacy may not be updated when regimen changes are made, which may lead to patients receiving incorrect

dosages or receiving their OOA at the wrong time.[11] These challenges from initial, and subsequent, prescriptions ultimately affect the patient. Patients often have more responsibility with OOA prescriptions than with traditional IV chemotherapy, including adherence, symptom management, other medication management, and financial management for treatment.[1,2,4,6,7] These healthcare system issues influence the patient in a way that is completely out of their control and may increase their workload and their overall distress. The healthcare system issues this work will examine include insurance delays, prescription errors, pharmacy errors, shipment delays, and any other situation identified by patients that caused a delay in receiving their OOA prescription.

Purpose

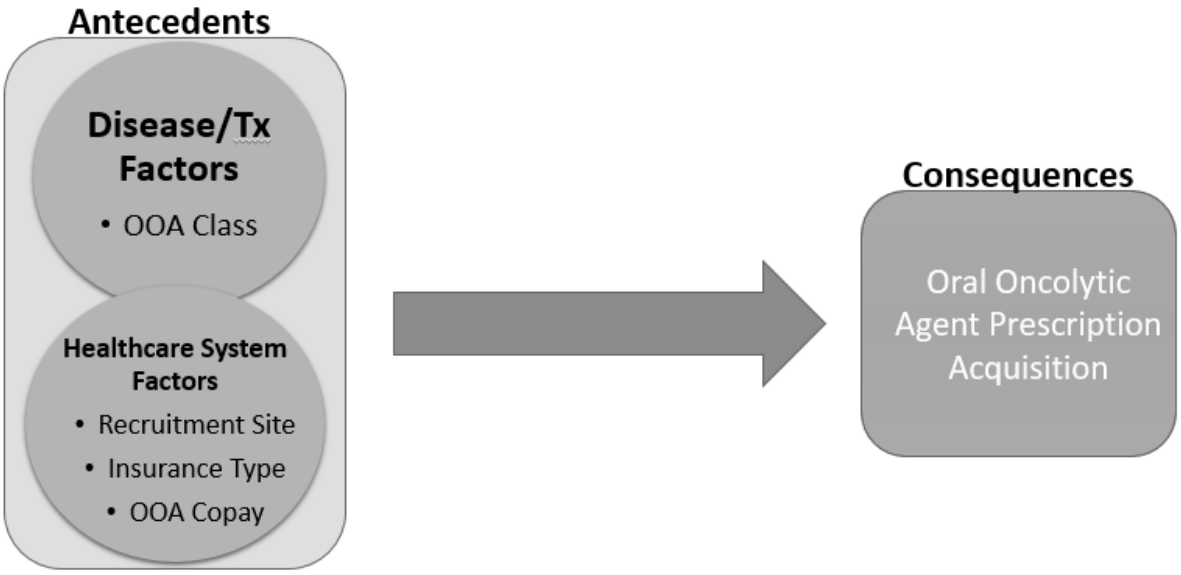
The purpose of this work is to identify the impact of the healthcare system on patient acquisition of OOAs. This work is a secondary analysis of a parent intervention trial focused on cancer patients newly prescribed OOAs, evaluating the time from prescription to patient acquisition. Two specific research questions guided this secondary analysis: 1) what is the time from prescription to receipt of OOAs for patients in the parent intervention study; and 2) how might type of insurance, OOA copay, patient recruitment site, and oral oncolytic drug class predict the time from prescription to receipt of OOAs? Guided by the Burden of Treatment Morbidity (BOTM) Model (Figure 1), the focus of this dissertation, this exploratory work examined the trial population for prescription acquisition challenges identified within the literature.

Conceptual Model

The Burden of Treatment Morbidity (BOTM) Model guides this chapter. An adaptation of the overall dissertation model will highlight the specific components of the BOTM being used (**Figure 3.1**). The adaptation of the BOTM model utilizes the two antecedent categories (disease/treatment factors and healthcare system factors) and the consequence of patient OOA acquisition. Oral oncolytic agent class is included for disease/treatment factors, and recruitment site, insurance type, and OOA copay are included for healthcare-system factor antecedents.

The primary outcome of this work is the patient time to acquisition from initial OOA prescription. Because this work is looking at the direct predictive influence of the antecedents on the consequence, the moderation of burden of treatment was excluded from the BOTM adaptation for this chapter.

Figure 3.1. Burden of Treatment Acquisition Analysis Model



Methods

This work was a secondary, longitudinal data analysis of a randomized-controlled trial that tested adherence and symptom management interventions in cancer patients that had been newly prescribed OOAs. The parent study, *Improving Adherence to Oral Cancer Agents and Self Care of Symptoms Using an IVR*, funded by the National Cancer Institute (1Ro1CA162401-O1A1), was an eight week two-arm, multisite randomized controlled trial (RCT).[18] with concluding observations at 12 week to determine sustainability. The experimental arm received a weekly symptom assessment with referral to a symptom management toolkit for symptoms ≥4/10, and an adherence intervention comprised of daily reminders, using an automated

interactive voice response (IVR) system. Control patients received standard care without referrals to a toolkit or reminder calls.

Sample

Parent Study Sample. Participants were recruited from six NCI-designated comprehensive cancer centers across the Midwest United States. Patients agreed to enroll in the study by signing a consent form, and could withdrawal at any point during the study. Inclusion Criteria for the parent study: Patients were to be 21 years or older; speak English; newly prescribed one of the designated FDA-approved oral oncolytics (Appendix A); Eastern Cooperative Oncology Group (ECOG) performance of 0-2 or Karnofsky score of ≥50 (Appendix B)[19,20] and actively receiving cancer treatment from one of the participating cancer centers. Exclusion Criteria: Patients were excluded if they had difficulty hearing on the telephone; limited or no access to a touch- tone phone; cognitive deficits, as determined by recruiters; or receiving hospice care.

In the parent study, 482 patients were screened for eligibility, with 438 being eligible, and 322 of these patients consented for the study. Of the consented patients, 272 patients completed the baseline interview and were then randomized into one of the two arms (Appendix C). Institutional review boards (IRB) at the study center and each recruitment site approved the study and all protocols.

Data Collection. Data were collected over the phone by trained interviewers at baseline, 4, 8, and 12 weeks. Interviewers collected information including OOA prescription information and pill counts, demographics, insurance coverage, social support, symptoms, multimorbid conditions, and interactions with healthcare providers. Data were also collected during the experimental group's daily reminder calls, as well as at the automated weekly, symptom calls. After patients completed the study, or attrited, trained abstractors at the respective cancer centers completed medical record audits (MRA) (Appendix D). Quality assurance checks were undertaken for every MRA, as well as randomly selected interviews each month for all patient interviewers.

Secondary Data Sample. All 272 participants that completed the baseline interview of the parent study will be included in this secondary data analysis. Participants will not be differentiated by experimental/control groups, since the intervention did not influence the outcome of time to acquisition of OOAs.

Measures

Table 3.1. includes an explanation of all included variables and measures. Patient demographic information was collected at enrollment and the baseline interview; this included age, sex, race, educational level, employment, and marital status (Appendix E). These demographic variables used will provide an overview of the sample of the secondary analysis. The primary variables used in this work are information gathered from both the patient telephone interviews and the MRAs. These variables include OOA drug class, insurance type, recruitment site, whether or not participants had an OOA copay, and the time from prescription to receipt of OOAs. All of the predictor healthcare system variables used in the model are categorical, including: OOA drug class (4 levels), insurance type (2 levels), recruitment site (5 levels), and OOA copay (2 levels).

The outcome variable of the model was the acquisition of the OOA. This was the patient report of the number of days from initial OOA prescription until the patient received the OOA in his/her hands. Days to receipt is a continuous variable for this work. Some patients were unable to recall the number of days from prescription to receipt. For these cases, the prescription date from the MRA to the patient reported date for when the participant started taking the OOA equates the days to receipt.

Table 3.1. Secondary Data Analysis OOA Acquisition Variables

Construct	Measures	Description
Patient Demographics	Age, Sex, Race, Education Level, Employment, and Marital Status	Patient reported during screening and baseline interview
Disease/ Treatment Factors	OOA Medication Class	Four categories: cytotoxics, kinase inhibitors, sex hormone inhibitors, other
Healthcare System Factors	Primary Insurance Type	Two categories: government or commercial/private
	Oral Oncolytic Out of Pocket (OOP) Cost	Yes/No
	Patient Recruitment Site	Five categories: Site A, Site B, Site C, Site D, and other
Outcome Variable	Time to Initial Acquisition	Number of days between the initial OOA prescription and when patient received the OOA (continuous)

Data Analysis

Frequencies of sample characteristics were summarized with descriptive statistics. In order to standardize the data and reduce skewness, a square root (sqrt) transformation was used for the outcome variable, days to receipt. Descriptive statistics were used to report the unadjusted means for the initial values of days to receipt and square root values of days to receipt. These means were reported by the healthcare system factor variables and OOA drug class.

To answer research question 2, how the healthcare system variables might predict the days to receipt of OOAs, a three-way ANOVA model was used. All two-way interactions and a three-way interaction between OOA drug class, OOA copay, and insurance type were included. Patient recruitment site was also included in the model as a main effect. Three-way and two-way interactions were examined for statistical significance at 95% level. F-values were calculated for simple interaction effects of OOA copay and insurance type by splitting the file and examining the interaction effects by each OOA drug class. In order to calculate the new f-values, the new mean squares (MS) were divided by the MS for the error term from the original

ANOVA model. These f-values were then tested for significance based on degrees of freedom (df) for simple interaction and total df for each OOA drug class within the split file model.

Results

The secondary analysis sample included all 272 participants from the parent trial that completed the baseline interview. The sample was evenly split between males and females and had a mean age of 61 years (**Table 3.2**.). Breast and colorectal were the two most common sites of cancer within the trial, comprising 36% of the sample. Leukemia was the most common of the hematologic malignancies (leukemia, lymphoma, and myeloma). Fifty-seven percent of the sample's primary form of insurance was government coverage, which included Medicare, Medicaid, and Veterans Affairs (VA). The rest of the sample's insurance coverage primarily consisted of self or spouses' coverage through their current or former employer. At intake, 53% of the sample had an out of pocket (OOP) copay for their initial OOA prescription, with a mean cost of $258 (range $1-8300 USD). Of the 28 primary oral agents patients were prescribed, 82% were taking either a cytotoxic or a kinase inhibitor at the start of the trial. The University of Michigan Cancer Center was the largest recruitment site for the trial, making up over 41% of the sample that completed the intake interview.

The mean number of days from prescription to receipt of patients' initial OOA prescription was 9.73 days (range 0-135). Patients with private/commercial insurance had to wait on average 9.9 days to receive their initial OOA prescription, while those with government insurance had an average acquisition time of 9.61 days (**Table 3.2.**). Patients without an OOA copay had a slightly longer wait time than those with a copay, 10.32 and 9.47 days, respectively. Patients prescribed other OOAs or kinase inhibitors experienced longer wait times, 11.75 days and 10.54 days, respectively. Those patients treated at recruitment site D waited on average 12.79 days to receive their OOAs, while all other cancer centers saw averages below the sample mean (9.73). With the range of days to receipt being quite large, a square root

transformation was implemented to create the square root (Days to Receipt) variable. The resulting square root sample mean was 2.56 days (SD 1.73).

A three-way analysis of variance (ANOVA) was conducted on the influence of healthcare system factor independent variables and OOA drug class on the number of days to receipt of OOAs (**Table 3.4.**). The three-way interaction between OOA copay, insurance type, and OOA drug class yielded a significant result, F (3, 232) = 3.612, p .01. Given the significant three-way interaction, simple interaction effects of OOA copay and insurance type by OOA drug class were analyzed. The following F values resulted: cytotoxics, F (1,78) = 0.548, p .46; kinase inhibitors, F (1, 114) = 6.709, p .01; sex hormone inhibitors, F (1, 19) = 7.879, p .01; and other, F (1,11) = 0.417, p .06. Additionally, there was a significant main effect of insurance type on sqrt(days to receipt), F (1,232) = 5.445, p .02.

Figure 3.2 displays the plots of simple interaction effects of OOA copay and insurance type on sqrt(days to receipt) by OOA drug class. In addition to the unadjusted initial values of days to receipt and unadjusted sqrt(days to receipt), **Table 3.3.** shows the estimated marginal means (least square means) for each level of the healthcare system factor independent variables. When taking into account the other healthcare system variables, there were slight changes in the estimated marginal square root means from the unadjusted square root means. Most notably, patients having government insurance coverage saw a longer number of days to receipt of OOAs when taking into account of variables within the ANOVA model.

Discussion

Advances in cancer treatment have led to a shift in the setting of the delivery of cancer care. As opposed to chemotherapy being administered via IV in a controlled setting, the increased prescription of OOAs have allowed more cancer patients to self-administer their chemotherapy in the home. Although OOAs provide some advantages for patients, OOAs are not without their drawbacks. With a substantial number of OOAs being approved by the FDA within the last years, insurance approval and the restrictions on facilities that are able to fill OOA prescriptions

have become challenges for providers and patients. This secondary analysis showed that cancer patients had to wait on average nearly 10 days from the time of provider prescription until they received their OOA. Nearly 23% of the sample received their OOA prescription on the day it was prescribed or the next day. Twenty-six patients had to wait three weeks or more to receive their medication, with one patient waiting 135 days. This wait time suggests that there may be barriers to patients receiving their OOA prescriptions in a timely manner. Insurance approval and specialty pharmacy fill times have been cited in previous works as primary contributors to the wait time of cancer patients in receiving their OOAs.[8,11,13,16]

The process from oncology provider prescription of OOAs to when the patient receives the medication and can begin treatment is a bit different from traditional IV chemotherapy. Unlike IV chemotherapy, which is billed under medical, OOAs are billed under the pharmacy benefit portion of patients' insurance coverage.[16] After provider prescription of an OOA, the oncology clinic or hospital must submit the necessary documentation the patient's insurance for approval. The amount of time for insurance approval may differ by type of insurance, insurance provider, and state in which the patient is receiving treatment.[8,13,14,21] This study found that insurance type might influence the time to receipt of OOAs, depending on whether or not individuals had a OOP copay and the OOA drug class that was prescribed. After insurance approves patients' OOAs, they may or may not have an OOP expense to cover the prescription. With several OOAs costing in excess of $100,000 (USD) per year before insurance,[22] cancer patients may take on a financial burden to cover the OOA copay.

Although more than 50% of the sample reported having an OOP copay, this research team believes that the number of patients that had some cost after insurance approval was higher. The reason for this is that many patients received financial assistance, either patient-assistance programs offered by drug companies that sell their specific OOA. The sample mean copay was $258 (USD), however the median copay was only $25. Dependent on insurance type and OOA drug class, OOP copay influenced the time to receipt of OOAs within this study. Given

the large pre-insurance costs of most OOAs, this research team believes that, along with insurance coverage, financial assistance provided a great relief for patients in either reducing or eliminating OOP copays. Unfortunately, patients may not be able to receive financial assistance for the duration of their treatment, and at some point, will have to make difficult financial decisions.

Not all patients found it feasible to pay for the OOP cost of their OOA prescription. During patients interviews within the parent trial, some patients discussed having to make difficult decisions in order to pay for their OOAs. Some patients mentioned having to borrow from their retirement funds or social security, borrowing money from a loved one, and taking out additional loans. Other patients stated that they or a spouse had to continue working in order to maintain insurance coverage or a viable income, even though they would have preferred to leave the workforce.

After receiving insurance approval and finding a way to pay for their OOAs, cancer patients need to find a way to get the medication in their hands. OOA prescriptions cannot be filled as simply as other chronic condition medications. Oral agents can only be distributed by on-site hospital pharmacies, specialty pharmacies, and mail-order pharmacies.[8,13] If patients are being treated at a larger medical center, they may be able pick up their prescription with each oncology visit, but a substantial number of patients rely on mail-order pharmacies to fulfill their OOA prescriptions. Being treated at a hospital or cancer center with pharmacies that fill OOA prescriptions can drastically reduce the patient acquisition time. This may have been a contributor to the longer acquisition times for patients treated at Site D.

In a previous study, pharmacy fulfillment and delivery of OOAs accounted for the longest portion of the OOA acquisition process.[8] This secondary analysis did not have data specific to each component of the OOA acquisition process, but interviewers were able to note examples of patients encountering delays with pharmacy fulfillment and delivery during the parent trial. Some patients reporting receiving the wrong dose or wrong label on the medication bottle,

having the wrong name on the package, receiving their medication after the expected date, and concerns were expressed about expensive medications being left out in the open when delivered. These situations contribute to the delay in starting new treatment or continuing on vital cancer treatment.

Limitations

This secondary analysis was limited in the following ways, due to the available data from the parent trial. First, the outcome measure of days to receipt of OOAs was based on patient report. Although this research team believes the data to adequately depict the experiences of the patients in the trial, not all patient accounts may have been accurate in recalling the days from prescription to receipt. Another limitation of the data is only having one endpoint to describe the full acquisition process, as opposed to being able to break down the number of days for each phase of the process. Participants were recruited from NCI-designated comprehensive cancer centers across the Midwest United States, and therefore, may not reflect the experiences of patients treated at clinics or hospital systems from other parts of the country or that are not comprehensive cancer centers. This study did not take into account whether patients were fulfilling their OOA prescription through a specialty pharmacy, at their medical center/clinic, or through a mail-order pharmacy. Finally, this secondary analysis only described the time to receipt of the initial OOA prescription. Most patients are prescribed OOAs indefinitely, so additionally work is needed to look at times to receipt of subsequent refills.

Conclusions

The purpose of this study was to determine the length of time cancer patients waited to receive their OOAs from the time of initial written prescription, and to determine what factors might influence this time to drug acquisition. This study showed that the amount of time patients must wait before receiving their initial prescription might vary depending on their type of insurance and whether or not they had a copay. Patients' treatment location and where they fulfill their prescription may also play a role in their time to acquisition. Oncology nurses should

communicate with patients that they might be waiting some time to receive their OOAs after the initial prescription. Oncology nurses should understand the process of fulfilling an OOA prescription, so that they are able to educate patients to help expedite the process or to identify when issues arise in the acquisition of OOAs. Nurses and other providers should also follow up with patients at each oncology clinic visit to ensure that patients are not encountering any issues with subsequent refills. In addition to communicating patients, providers should be communicating with one another, insurance companies, OOA manufacturers, and pharmacies to ensure prompt delivery to patients. Such communication may be prescriber to nurse at the time of prescription to begin documentation as early as possible, as well as providers following up with insurance companies and outside pharmacies to speed up portions of the process.

Future work should examine each phase of the OOA acquisition process and continue to follow up with patients through subsequent refills. This work would allow researchers and providers to identify which phases of the acquisition process account for the greatest amount of time. Additionally, an intervention trial should be conducted testing the use of a clinical liaison, such as an oncology nurse, to help guide cancer patients through the acquisition process and maintain frequent contact with patients to assist if issues were to arise. This work may help to enact policies that regulate each step of the OOA acquisition process, in order to promptly deliver OOAs to cancer patients. These policies could lead to changes in documentation or staffing at certain phases of the process, which may work to expedite the acquisition process. These changes may focus particularly on insurance coverage and payments, as well as how specialty pharmacies and clinics work with insurance companies and patients to fulfill OOA prescriptions. Cancer patients prescribed OOAs, particularly solid tumor patients that have gone through several forms of treatment, are at a critical point in their care trajectory. Future research and practice need to work to delivery patients proper care in a timely manner. Not receiving their OOAs in a timely manner can not only be frustrating for patients, but not being able to start

treatment or continue treatment as prescribed may lead to poor disease control and worsening outcomes for patients.

Table 3.2. Descriptive Statistics for the Secondary Analysis Study Sample (N=272)

Characteristic	Frequency n (%)
Age (Mean Years, SD)	61.38 (12.22)
Sex	
Male	136 (50)
Female	136 (50)
Race	
African American	22 (8)
Caucasian	241 (89)
Other/unknown	7 (3)
Level of education	
High school or less	71 (26)
Some college or completed college	150 (55)
Graduate or professional degree	49 (18)
Unknown	2 (1)
Employment status	
Employed	88 (32)
Unemployed	184 (68)
Marital status	
Married	167 (61)
Not married	105 (39)
Insurance type	
Government	154 (57)
Private/Commercial	118 (43)
Oral agent copay	
Yes	143 (53)
No	114 (42)
Don't know	15 (5)
Recruitment site	
Site A	41 (15)
Site B	111 (41)
Site C	37 (14)
Site D	58 (21)
Other	25 (9)
Drug category	
Cytotoxic agents	95 (35)
Kinase inhibitors	127 (47)
Sex hormone inhibitors	27 (10)
Other	23 (8)
Site of Cancer	
Brain	2 (1)
Breast	57 (21)
Colorectal	41 (15)
Esophageal	3 (1)
GI	17 (6)
Leukemia	16 (6)
Liver	12 (4)
Lung	10 (4)
Lymphoma	3 (1)
Melanoma	8 (3)
Myeloma	7 (3)
Pancreatic	27 (10)
Prostate	26 (10)
Renal	24 (9)
Sarcoma	15 (5)
Other	4 (1)

Table 3.3. Unadjusted and Adjusted Mean Days to Receipt of OOAs by Healthcare System Factors

Healthcare System Factors	Unadjusted Mean (SD)	Unadjusted Sqrt Mean (SD)	Estimated Marginal Mean Sqrt (SE)
Insurance Type			
Government	9.61 (15.70)	2.53 (1.80)	2.96 (0.22)
Private/Commercial	9.90 (13.11)	2.69 (1.63)	2.22 (0.24)
OOA Copay			
Yes	9.47 (12.84)	2.65 (1.56)	2.66 (0.21)
No	10.32 (16.98)	2.56 (1.95)	2.53 (0.25)
Recruitment Site			
Site A	8.83 (6.98)	2.69 (1.27)	2.74 (0.31)
Site B	8.21 (5.78)	2.65 (1.09)	2.48 (0.33)
Site C	12.79 (13.23)	3.15 (1.72)	3.10 (0.27)
Site D	9.32 (19.39)	2.30 (2.02)	2.30 (0.22)
Other	8.21 (7.45)	2.48 (1.46)	2.40 (0.38)
OOA Drug Class			
Cytotoxic	8.15 (9.30)	2.46 (1.45)	2.67 (0.22)
Kinase Inhibitors	10.54 (15.63)	2.65 (1.88)	2.61 (0.17)
Sex Hormone Inhibitors	10.00 (6.13)	2.90 (1.29)	2.11 (0.44)
Other	11.57 (28.67)	2.49 (2.38)	2.98 (0.42)
Total	9.73 (14.54)	2.56 (1.73)	2.59 (0.17)

Abbreviations: OOA, oral oncolytic agent; SD, standard deviation; SE, standard error

Table 3.4. ANOVA Results for Effect of Healthcare System Factors on Days to Receipt of OOAs

	df	Mean Square	*F*	*P*
Variable				
Recruitment Site	4	4.666	1.663	0.15
OOA Copay	1	0.430	0.153	0.69
Insurance Type	1	15.280	5.446	0.02
OOA Drug Class	3	1.877	0.669	0.57
Copay*Insurance Type	1	34.217	12.195	<0.01
Copay*Class	3	3.539	1.261	0.29
Insurance Type*Class	3	8.470	3.019	0.03
Copay*Insurance Type*Class	3	10.134	3.612	0.01
Error	232	2.806		
Total	252			

Abbreviations: OOA, oral oncolytic agent; df, degrees of freedom

Figure 3.2. ANOVA Simple Interaction Effects Plots on OOA Drug Class

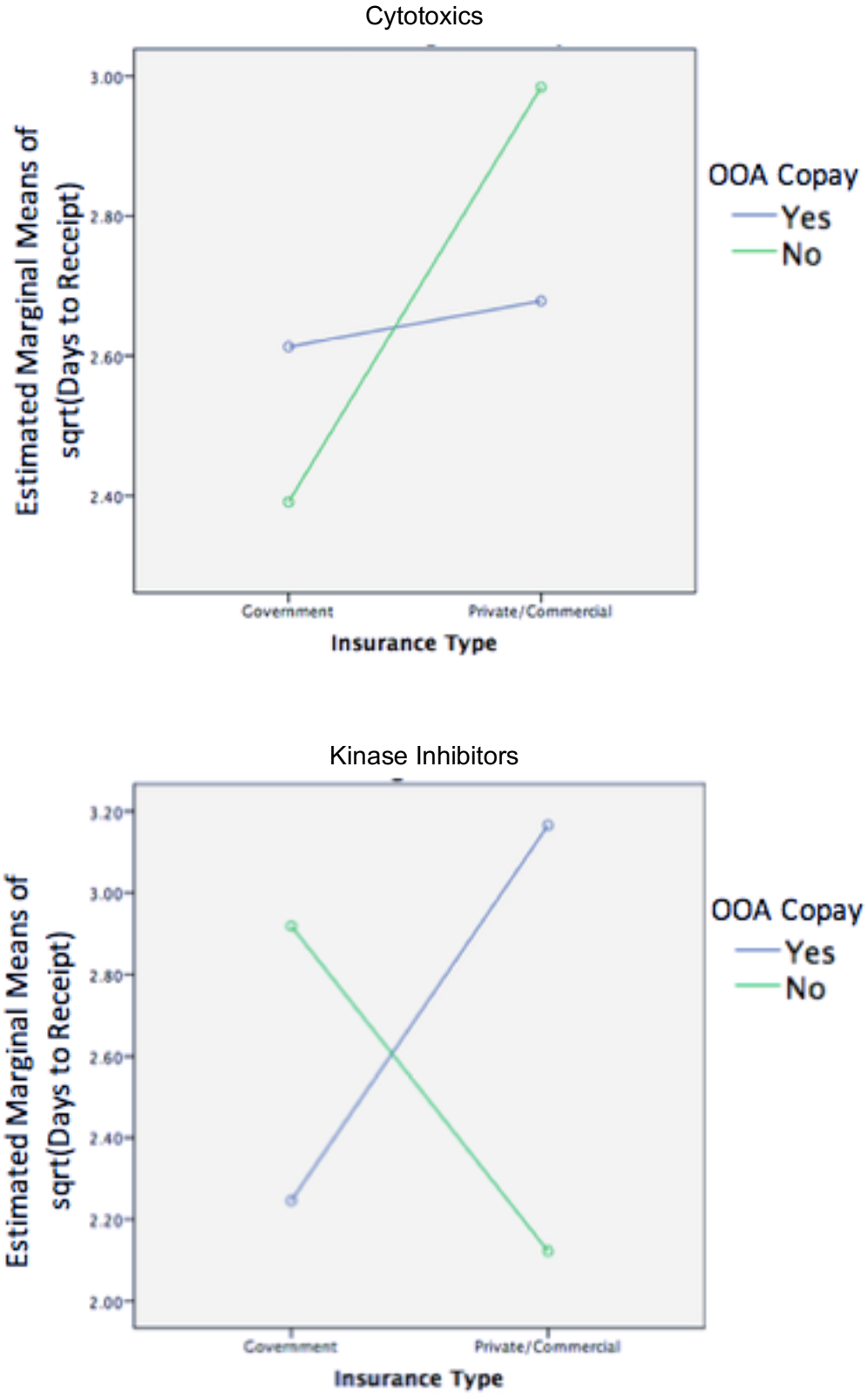
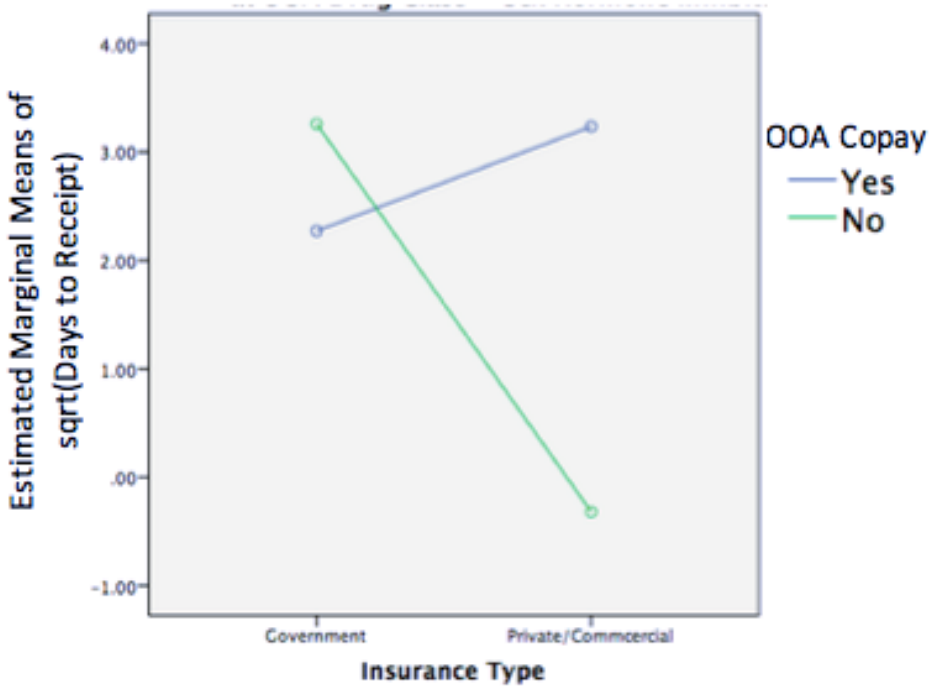
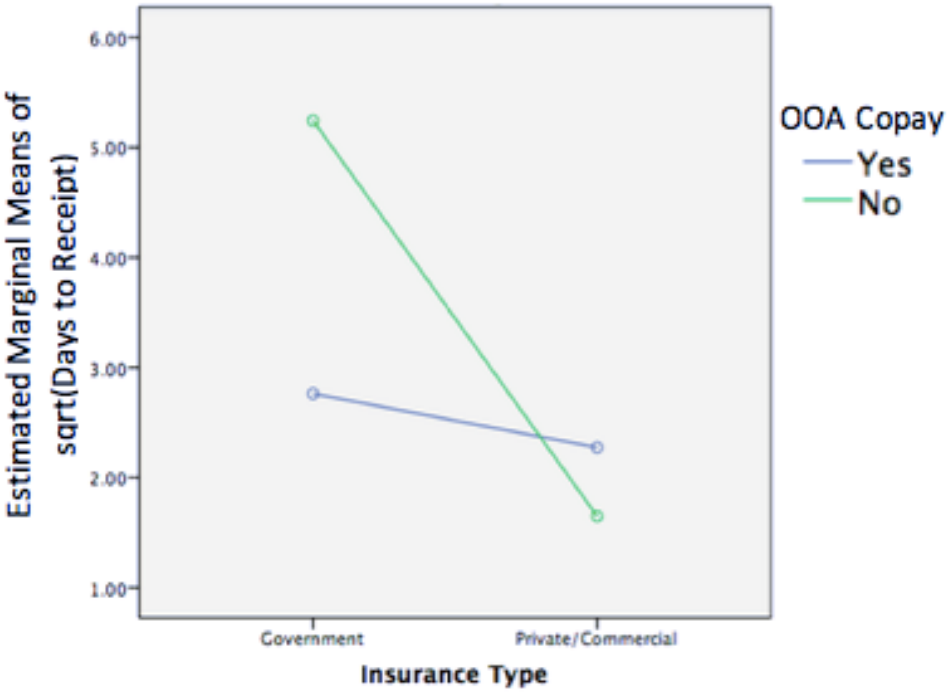


Figure 3.2. (cont'd)

Sex Hormone Inhibitors



Other



APPENDICES

APPENDIX A: FDA Approved Oral Oncolytic Agents Included in the Parent Study

Table 3.5. FDA Approved Oral Oncolytic Agents Included in the Parent Study

Oral Oncolytic Agents Organized Alphabetically by Trade Name	
Afinitor (Everolimus)	Stivarga (Regorafenib)
Bosulif (Bosutinib)	Sutent (Sunitinib)
Gilotrif (Afatinib)	Tafinlar (Dabrafenib)
Gleevec (Imatinib)	Tarceva (Erlotinib)
Ibrance (Palbociclib)	Tasigna (Nilotinib)
Imbruvica (Ibrutinib)	Temodar (Temozolomide)
Inlyta (Axitinib)	Tykerb (Lapatinib)
Lenvima (Lenvatinib)	Votrient (Pazopanib)
Lonsurf (Tipiracil & Trifluridine)	Xalkori (Crizotinib)
Lynparza (Olaparib)	Xeloda (Capecitabine)
Nexavar (Sorafenib)	Xtandi (Enzalutamide)
Pomalyst (Pomalidomide)	Zydelig (Idelalisib)
Revlimid (Lenalidomide)	Zykadia (Ceritinib)
Sprycel (Dasatinib)	Zytiga (Abiraterone acetate)

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX B: Eastern Cooperative Oncology Group Scale of Performance Status & Karnofsky Status Performance Scale

Table 3.6. Eastern Cooperative Oncology Group Scale of Performance Status & Karnofsky Status Performance Scale

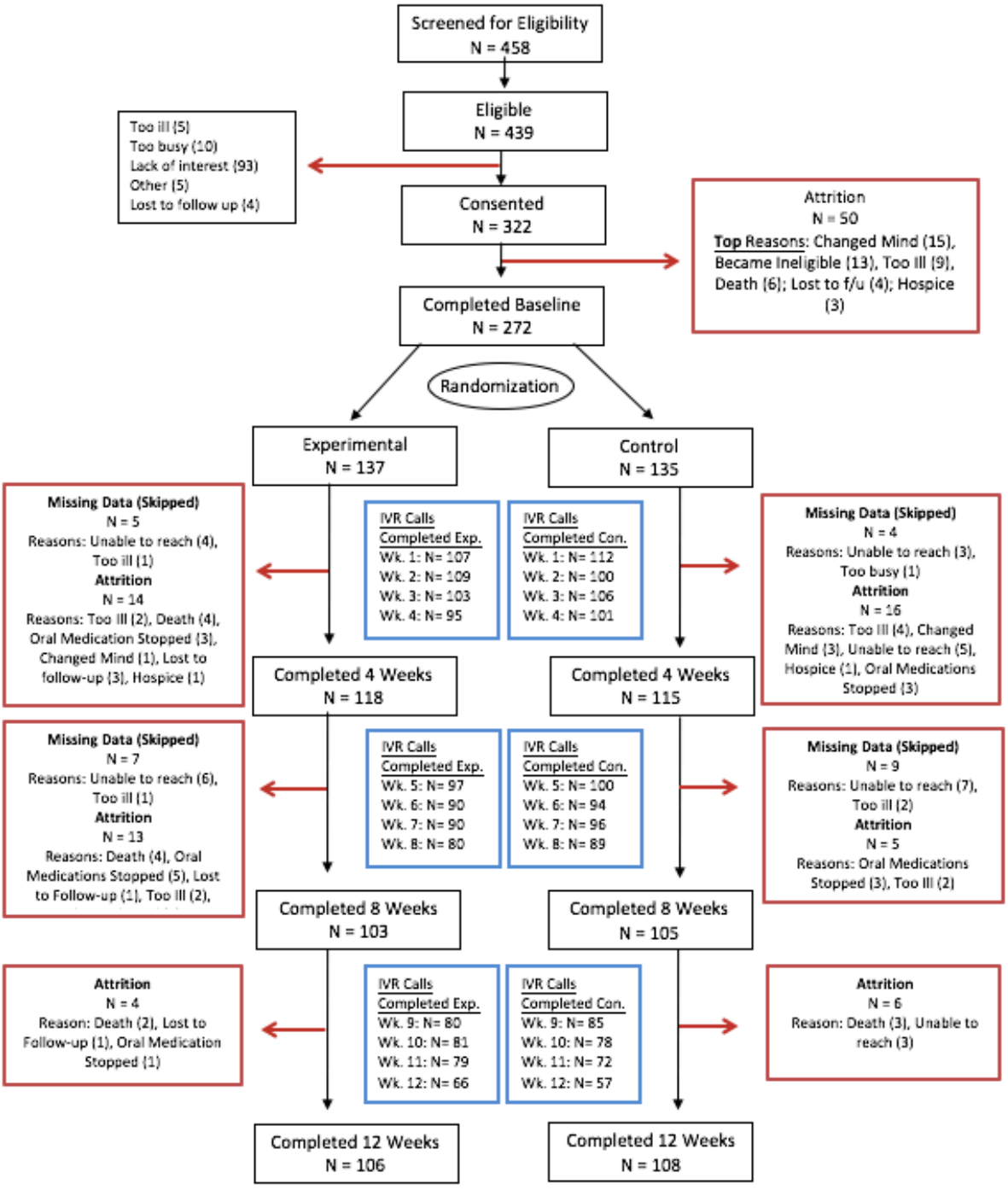
WHO/ECOG Grade	WHO/ECOG Activity	Karnofsky Grade	Karnofsky Activity
0	Fully active, able to carry on all normal activities without restriction	100%	Normal no complaints; no evidence of disease
		90%	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80%	Normal activity with effort; some sign or symptoms of disease
		70%	Cares for self; unable to carry on normal activity or do active work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60%	Requires occasional assistance, but is able to care for most personal needs
		50%	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40%	Disabled; requires special care and assistance
		30%	Severely disabled; hospitalization admission is indicated, although death not imminent
4	Completely disabled. Cannot carry on any self-care, totally confined to bed or chair.	20%	Very sick; hospital admission necessary; active support treatment is necessary
		10%	Moribund; fatal processes progressing rapidly
5	Dead	0%	Dead

Karnofsky DA. The clinical evaluation of chemotherapeutic agents in cancer. *Evaluation of Chemotherapeutic Agents.* 1949:191-205.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology.* 1982;5(6):649-655.

APPENDIX C: Parent Study CONSORT Flow Chart

Figure 3.3. Parent Study CONSORT Flow Chart



Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX D: Parent Study Medical Record Audit

BACKGROUND

Patient Initials: _____ **Gender:** □ Male □ Female

Audit Start Date __/__/__/____(mm/dd/yyyy) ***(1 month prior to consent date)*** **Audit End Date** ___/____/____(mm/dd/yyyy) ***(12 week interview date)***

Date of Audit: _____ **Abstractors Initial:** _____

Notes of special alerts for searching medical record for this patient e.g., patient reported surgeries or hospitalizations during the audit period:

Performance Site (*check one*):

□ Breslin □ Indiana University □ Northwestern □ Ohio State University
□ Sparrow □ University of Michigan □ University of Pittsburgh □ Yale
□ _____(other)

Date of initial diagnosis for the cancer being treated (mm/dd/yyyy) _____

Patient Height _____(in) **Patient Weight** _____(lbs) **Date of Height/Weight**_____

If patient died during the study, date of death (mm/dd/yyyy) ____

Site of Current Cancer Diagnosis (*check one, if more than one diagnosis, check site being treated with an oral agent*):

□ Breast □ Colon/Rectal □ Small Cell Lung □ Pancreas □ Lymphoma
□ Prostate □ Gastrointestinal □ Kidney □ Leukemia □ Non Small Cell Lung
□ Unknown □ Other (*write in*) _____

If there is a second primary cancer (non metastasized) (*check one*):

□ Breast □ Colon/Rectal □ Small Cell Lung □ Pancreas □ Lymphoma
□ Prostate □ Gastrointestinal □ Kidney □ Leukemia □ Non Small Cell Lung
□ Unknown □ Other (*write in*) _____

Stage of Disease (*check one*): □ I □ II □ III □ IV □ Not Staged

Stage of Disease at study start: □ I □ II □ III □ IV □ Not Staged

For Small Cell Lung only: □ Limited □ Advanced

TNM stage (*fill in number*): T _____ N _____ M _____

If unable to record TNM, check one below:
□ Localized □ Metastatic

Additional Information (i.e., grade, etc.): Grade (*write in*) _____

Record location of metastasis (*check all that apply*): □ Brain □ Lung □ Bone □ Liver
□ Other (*write in*) _____

Is this diagnosis a recurrent disease (*disease free \ remission period*)? (*check one*)
□ Yes □ No □ Don't know

Did progression of the disease occur during this audit period? □ Yes □ No □ Don't know

Was the patient undergoing treatment during the month prior to starting on Oral Agents? □ Yes □ No

Did the patient receive **infusion chemotherapy** in the audit period? □ Yes □ No □ Don't know

If yes, when did he/she **START infusion chemotherapy**? *(write in)* If yes, when did he/she **END infusion chemotherapy**? *(write in)* (*NOTE leave END date blank if ongoing*)
___/___/____(mm/dd/yyyy)
___/___/____(mm/dd/yyyy)

Infusion chemotherapy drug name(s): *(write in)*_____

If stopped, reason stopped **infusion chemo**? □ Side Effect □ Complication □ Completed

Has patient received **radiation** in the audit period? □ Yes □ No □ Don't know

If yes, when did he/she **START radiation**? *(write in)* If yes, when did he/she **END radiation**? *(write in)* (*NOTE leave END date blank if ongoing*)
____/____/_____(mm/dd/yyyy)
____/____/_____(mm/dd/yyyy

If stopped, reason stopped **radiation**? □ Side Effect □ Complication □ Completed

Did patient have **surgery** since starting oral agent? □ Yes □ No □ Don't know

If yes:
Date of surgery *(write in)* __/____(mm/yyyy) Procedure(s) *(write in)* _____
Date of surgery *(write in)* __/____(mm/yyyy) Procedure(s) *(write in)* _____

Patient visits to **Oncology clinic** during audit period:

Date ____/____/_____ (mm/dd/yyyy) Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy) Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy) Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy) Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy) Reason for visit _____ *(write)*

Patient **hospitalized** during audit period:

Date Admitted ___/___/___(mm/dd/yyyy) Date Discharged___/___/___(mm/dd/yyyy)
Date Admitted ___/___/___(mm/dd/yyyy) Date Discharged___/___/___(mm/dd/yyyy)
Date Admitted ___/___/___(mm/dd/yyyy) Date Discharged___/___/___(mm/dd/yyyy)

Patient visits to **ER / Urgent Care** during audit period:

Date ___/___/_____(mm/dd/yyyy) Reason for visit _____*(write in)*
Date ___/___/_____(mm/dd/yyyy) Reason for visit _____*(write in)*

Is there evidence of **screening for mutations prior** to starting oral agent? □ Yes □ No □ Don't know

If yes, check the appropriate box:

□ ALK (Lung)
□ BCR-ABL (T3151)
□ BRAF (Melanoma)
□ BRCA 1 or 2
□ DPYD
□ EGFR (Breast, Colon, Lung)
□ FISH
□ HER2 + or -
□ KIT
□ KRAS (Colon)
□ PDGFR
□ Ph+ Chromosome
□ TSCI1 or 2
□ V600E/K
□ Other mutation *(write in)*_____
□ Other mutation *(write in)*_____

Where did the patient get their oral agent?

Hospital pharmacy □ Yes □ No □ Don't
Local pharmacy (CVS, Walgreen, etc.) □ Yes □ No □ Don't
Specialty Pharmacy □ Yes □ No □ Don't

Table 1: Cancer Protocols and Drugs during Audit Period: PROTOCOL 1

Name of Drug(s) in Protocol 1 (Injection, Infusion, Patch)	Date Prescribed	Dose or Injection (mg per pill or mg/ml)	No. Pills/Day or Injections, Infusions or Patches	Continuous Dosing	Start on Cycle Day	No. of Days On in a Cycle	Number of Days Off in a Cycle	Drug Ongoing	Discontinuation Permanent (P) or Temporary (T) & Date(s)	If stopped (changed), Why? (choose Reason Number below)
Drug 1 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 1	__/__/__			**Yes / No**				**Yes / No**		
Drug 2 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 2	__/__/__			**Yes / No**				**Yes / No**		
Drug 3 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 3	/ /			**Yes / No**				**Yes / No**		

Use this table to determine the **Reason Number** to complete the final column 'If Stopped, changed or discontinued...' above. Write in all that apply

#	Reason	#	Reason	#	Reason - Delay of Drugs / Stoppage
1	Anemia	12	Dyspnea (Shortness of Breath)	23	Peripheral Neuropathy
2	Anorexia	13	Edema, Limb	24	Pruritus / Skin Problem / Rash
3	Arthralgias/Myalgias	14	Fatigue (Asthenia, Lethargy, Malaise)	25	Pulmonary problems
4	Bleeding/Hemorrhage	15	Febrile Neutropenia	26	Renal Failure
5	Cardiac Problems	16	Fever without Neutropenia	27	Thrombocytopenia (low platelets)
6	Completed prescribed protocol	17	Insomnia (Difficulty Sleeping)	28	Protocol completed
7	Constipation	18	Mucositis (Stomatitis)	29	Patient decision to stop treatment
8	Cost of Medication	19	Nausea and or vomiting	30	Patient entered hospice (date) / /
9	Cough	20	Neutropenia	31	**Disease progression—no response to therapy**
10	Deep Vein Thrombosis	21	Pain	32	Drug was changed
11	Diarrhea	22	Pericardial Effusion	33	Other *please write in*

Table 1: Cancer Protocols and Drugs during Audit Period: PROTOCOL 1

Name of Drug(s) in Protocol 1 (Injection, Infusion, Patch)	Date Prescribed	Dose or Injection (mg per pill or mg/ml)	No. Pills/Day or Injections, Infusions or Patches	Continuous Dosing	Start on Cycle Day	No. of Days On in a Cycle	Number of Days Off in a Cycle	Drug Ongoing	Discontinuation Permanent (P) or Temporary (T) & Date(s)	If stopped (changed), Why? (choose Reason Number below)
Drug 1 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 1	__/__/__			**Yes / No**				**Yes / No**		
Drug 2 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 2	__/__/__			**Yes / No**				**Yes / No**		
Drug 3 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 3	/ /			**Yes / No**				**Yes / No**		

Use this table to determine the **Reason Number** to complete the final column 'If Stopped, changed or discontinued...' above. Write in all that apply

#	Reason	#	Reason	#	Reason - Delay of Drugs / Stoppage
1	Anemia	12	Dyspnea (Shortness of Breath)	23	Peripheral Neuropathy
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Table 1: Cancer Protocols and Drugs during Audit Period: PROTOCOL 1

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Drug 1 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 1	__/__/__			**Yes / No**				**Yes / No**		
Drug 2 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 2	__/__/__			**Yes / No**				**Yes / No**		
Drug 3 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 3	/ /			**Yes / No**				**Yes / No**		

Use this table to determine the **Reason Number** to complete the final column 'If Stopped, changed or discontinued...' above. Write in all that apply

#	Reason	#	Reason	#	Reason - Delay of Drugs / Stoppage
1	Anemia	12	Dyspnea (Shortness of Breath)	23	Peripheral Neuropathy
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8	Cost of Medication	19	Nausea and or vomiting	30	Patient entered hospice (date) / /
9	Cough	20	Neutropenia	31	**Disease progression—no response to therapy**
10	Deep Vein Thrombosis	21	Pain	32	Drug was changed
11	Diarrhea	22	Pericardial Effusion	33	Other *please write in*

PATIENT COMPLICATIONS, TOXICITY AND SIDE EFFECTS (C/SE) DURING CURRENT ORAL AGENT AUDIT TREATMENT PERIOD

Table 2 is a summary from the NCI toxicity criteria that you may use for all complications and side effects (C/SE). Please date the C/SE. For all C/SE, please check and estimate toxicity if it is not stated explicitly then make grade not known (check box Grade Unknown).

PLEASE CHECK GRADE AT MOST SEVERE LEVEL AND DATE WHEN IT OCCURRED.

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	**Documented in chart? Yes / No**	**Date Noted in Chart**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade Unknown** *Check if not known*
1. Anemia			☐10.0/gdl or higher; 100g/L	☐8.0-10.0/gdl; <100-80 g/L	☐6.5-7.9/gdl; <80-65 g/L	☐<6.5/gdl; <65 g/L	☐
2. Anorexia			☐Loss of appetite without alteration in eating	☐Oral intake altered without weight loss or malnutrition; oral nutrition supplement	☐Weight loss or malnutrition (e.g., inadequate oral caloric or fluid intake); IV fluids or TPN	☐Life-threatening consequences	☐
3. Arthralgias/ Myalgias			☐Mild pain with inflammation	☐Moderate or severe, transient pain with swelling and inflammation	☐Severe, unrelenting pain with joint suffering; interfere with ADL	☐Immobility, unable to move	☐
4. Bleeding/Hemorrhage			☐Mild without transfusion; few symptoms <Male 4.7 – 6.1 million per MCL (write in levels) <Female 4.2 – 5.4 million per MCL (write in levels)	☐Symptomatic loss of 1 liter of blood	☐Transfusion indicated; 2 liters of blood	☐Catastrophic bleeding, major blood replacement	☐
5. Confusion/Hallucination			☐Mild disorientation or mild hallucinations / Perceptual distortions	☐Moderate disorientation limiting ADL / Moderate hallucinations	☐Severe disorientation limiting self care & safety / Severe & frequent hallucinations	☐Life threatening, totally unmanageable, threats of harm to self or others / Threats due to hallucinations, needs hospitalization	☐
6. Constipation			☐Mild	☐Moderate	☐Severe	☐Ileus> 96hrs	☐
7. Cough			☐Dry hacking	☐Dry cough, treatment needed	☐Unrelenting, interferes with sleep and ADL	☐Severe continuous wet cough	☐

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	**Documented in chart? Yes / No**	**Date Noted in Chart**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade Unknown** *Check if not known*
8. Dehydration			☐↑ Oral fluids indicated; dry mucous membrane; ↓ skin turgor	☐IV fluids indicated <24 hours	☐IV fluids indicated ≥24 hours	☐Life-threatening consequences (e.g., hemodynamic collapse)	☐
9. Diarrhea			☐↑ of 2-3 stools /d over pre-Rx	☐↑ of 4-6 stools/d moderate cramping nocturnal stools	☐↑ of 7-9 stools/d severe cramping incontinence	☐↑ of >10 stools/d parenteral support grossly bloody stools	☐
10. Dyspnea (shortness of breath)			☐Dyspnea on exertion, can walk 1 flight of stairs without stopping	☐Dyspnea on exertion unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping	☐Dyspnea with ADL	☐Dyspnea at rest; intubation/ventilator indicated	☐
11. Edema; limb, facial			☐5-10% inter-limb discrepancy in volume or circumference visible difference; swelling; pitting edema	☐>10-30% inter-limb discrepancy in volume or circumference apparent obstruction of anatomic structure; obliteration of skin folds	☐>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	☐Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	☐
12. Fatigue (asthenia, lethargy, malaise)			☐Mild fatigue over baseline	☐Causing difficulty performing ADL	☐Severe fatigue interfering with ADL	☐Disabling	☐
13. Febrile Neutropenia (ANC <1.0x109/L, fever >38.5°C)			☐38.0 – >39.0°C (100.4 – 102.2°F) with neutropenia	☐39.0 – >40.0°C (102.3 – 104.0°F) with neutropenia	☐ ≤40.0°C (≤104.0°F) for ≤24 hours with neutropenia	☐Life-threatening (e.g., septic shock, hypotension, acidosis) ≤40.0°C (≤104.0°F) for >24 hrs with hypotension	☐
14. Fever without Neutropenia			☐38.0 – >39.0°C (100.4 – 102.2°F)	☐39.0 – >40.0°C (102.3 – 104.0°F)	☐ ≤40.0°C (≤104.0°F) for ≤ 24 hours	☐ ≤104°F for 24 hours with shock like symptoms	☐
15. Hand and Foot Skin Reaction			☐Skin changes; no pain	☐Skin changes with pain; no functional interference; peeling, blisters	☐Skin changes interfering with function; pain, ulcers, edema	☐Disability due to function interference and pain	☐

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	**Documented in Chart? Yes / No**	**Date Noted in Chart**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade Unknown** *Check if not known*
16. Hyperglycemia			☐ 160 mg/dL; 8.9 mmol/L	☐ > 160-250 mg/dL; >8.9 – 12.9 mmol/L	☐ > 250-500 mg/dL; 13.9 – 27.8 mmol/L; hospitalization indicated	☐ > 500 mg/dL; >27.8 mmol/L; life-threatening consequences	☐
17. Insomnia (difficulty sleeping)			☐ Occasional, not interfering with function	☐ Interferes with function but not with ADL	☐ Frequent, interfering with ADL	☐ Disabling	☐
18. Memory impairment/ Cognitive Changes			☐ Not interfering with function	☐ Interferes with function, but not interfering with ADL	☐ Interfering with ADL	☐ Amnesia	☐
19. Mucositis / Stomatitis			☐ Erythema, painless ulcers, mild soreness	☐ Painful erythema, edema, ulcers can eat	☐ Painful erythema, edema, ulcers	☐ Parenteral or enteral support	☐
20. Nausea			☐ Able to eat but lack of appetite	☐ About to eat, diminished intake	☐ Unable to eat, 0 intake, inadequate fluids, dehydration, weight loss	☐ Life threatening	☐
21. Pain			☐ Mild, not interfering with function	☐ Moderate, interfering with function, but not interfering with ADL	☐ Severe, interfering with ADL	☐ Disabling	☐
22. Platelets (PLT) (x 1000/mm3)			☐ <75.0x10^9/L <75000/mm^3	☐ ≥50.0-<74.9x10^9/L ≥50000-<75000/mm^3	☐ ≥25.0-<50x10^9/L ≥10000-≤20000/mm^3	☐ <10.0x10^9/L-<25.0x10^9/L <10000/mm^3	☐
23. Pruritus			☐ Mild or localized	☐ Intense, widespread, little to no discomfort	☐ Widespread with discomfort	☐ Widespread, open and weeping discomfort	☐
24. Skin/Macular/Rash			☐ Scattered macular or popular rash or erythema that is asymptomatic	☐ Scattered macular or papular rash or erythema with pruritus or other symptoms	☐ Generalized symptomatic macular, popular, or vesicular rash	☐ Exfoliative or ulcerating dermatitis	☐
25. Vomiting			☐ 1 episode in 24 hours	☐ 2-5 episodes in 24 hours; IV fluids indicated <24 hours	☐ ≥6 episodes in 24 hours; IV fluids, or TPN indicated ≥24 hours	☐ Life-threatening consequences	☐

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	Documented in Chart? Yes / No	Date Noted in Chart	Grade 1	Grade 2	Grade 3	Grade 4	Grade Unknown *Check if not known*
26. WBC (Neutropenia - x100/mm3)			☐<3.0-3.9x10^9/L <3000/mm^3	☐<2.0-2.9x10^9/L ≥2000-2900/mm^3	☐<1.0-1.9x10^9/L ≥1000-<1900/mm^3	☐<1.0x10^9/L <1000/mm^3	☐
27. Other e.g. wound infections, neurological events, pathological fractures *(write in & describe)*							☐

DOCUMENTATION IN THE MEDICAL ELECTRONIC RECORD

Evidence of oral cancer medication not being available, or availability	□ Yes	□ No
Is there a record that patient received discussion about financial assistance for oral cancer medication (insurance or social worker)?	□ Yes	□ No
Is there evidence of any discussion of medication cost concerns with patient?	□ Yes	□ No
Is there any documentation of patient training or education about oral cancer medication?	□ Yes	□ No
If yes, was it a: Pharmacy	□ Yes	□ No
Patient education (classes or instruction)	□ Yes	□ No
Specialty pharmacy	□ Yes	□ No
Is there any documentation of adherence / non adherence with oral cancer medication?	□ Yes	□ No
Is there any documentation of follow up calls to check on patient's oral cancer medication, or any side effects from medication?	□ Yes	□ No

Complete Table 3

PRESCRIBED MEDICATIONS OTHER THAN CHEMO OR ORAL CANCER MEDICATIONS LISTED IN TABLE 1

Please list all medications (other than chemotherapy agents listed in Table 1) that were prescribed during the audit period, as well as medications that the patient was on for comorbid conditions during the audit period.

Table 3: Prescribed Medications

NAME OF DRUG	DATE PRESCRIBED

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX E: Parent Study Screening/Baseline Data Collection Tools

What is your highest level of education completed?
o No formal education
o Completed grade school
o Completed some high school
o Completed high school
o Completed some college or technical college or associate degree
o Completed college
o Completed graduate/professional degree (post baccalaureate degree)
o Refused

What is your current marital status?
o Never married
o Married
o Divorced/Separated o Widowed
o Living together
o Refused

What is your ethnic background?
o Hispanic or Latino
o Not Hispanic or Latino
o Unknown
o Refused

What is your race or ethnic background?
o American Indian or Alaskan Native
o African American or Black
o Asian
o Native Hawaiian or Pacific Islander o White
o More than one race
o Unknown
o Refused

Gender:
o Male
o Female

Ethnicity:
o Hispanic/Latino
o Not Hispanic/Latino

Screening Eligibility Form from Parent Study
(Collecting patient and disease characteristics)

Race (check all that apply):
o American Indian/Alaska Native
o Asian
o Native Hawaiian/Pacific Islander
o Black/African American
o White

Cancer Site:
o Breast
o Colorectal
o Gastrointestinal
o Leukemia
o Liver
o Lung
o Lymphoma
o Melanoma
o Myeloma
o Pancreatic
o Prostate
o Renal
o Sarcoma

Stage:
o I
o II
o III
o IV
o Other
If 'Other' write in stage: _____

On Concurrent IV chemotherapy?:
o Yes
o No
o If yes, medication and frequency:_____ o

On Concurrent Radiation?
o Yes
o No
o If yes, treatment name and frequency: _____

Patient Eligibility:
o Yes o No
(If NO to ANY of the questions below, patient is NOT eligible)

Can hear on telephone?
o Yes o No

Can read and understand English?

o Yes o No

21 or older?
o Yes
o No
o Age:_____

ECOG Performance status within 0-2 or Karnofsky performance status within 50-100?
o Yes
o No
o Score:_____

Has a land line/cell phone with touch pad numbers?
o Yes o No

Is on an eligible oral cancer medications?
o Yes o No

Eligibility:
o Eligible o Ineligible

Enrollment Status:
o Consented
o Refused
o Lost to follow-up

Reason, if refused:
o Too ill
o Too busy
o Lack of interest
o Other

Date Screened: _____ Recruiter Initials: _____

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

REFERENCES

REFERENCES

1. Bassan F, Peter F, Houbre B, et al. Adherence to oral antineoplastic agents by cancer patients: definition and literature review. *European Journal of Cancer Care.* 2014;23(1):22-35.

2. Hall AE, Paul C, Bryant J, et al. To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Critical Reviews in Oncology/Hematology.* 2016;97:247-262.

3. Hugtenburg JG, Timmers L, Elders PJ, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. *Patient Preference and Adherence.* 2013;7:675-682.

4. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. *Cancer Treat Rev.* 2014;40(1):102-108.

5. Conti RM, Fein AJ, Bhatta SS. National trends in spending on and use of oral oncologics, first quarter 2006 through third quarter 2011. *Health Affairs (Project Hope).* 2014;33(10):1721-1727.

6. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK. Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review. *JAMA Oncology.* 2018;4(1):105-117.

7. Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. *Cancer Treat Rev.* 2013;39(6):610-621.

8. Niccolai JL, Roman DL, Julius JM, Nadour RW. Potential Obstacles in the Acquisition of Oral Anticancer Medications. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2017;13(1):e29-e36.

9. Accordino MK, Hershman DL. Disparities and challenges in adherence to oral antineoplastic agents. *American Society of Clinical Oncology educational book / ASCO American Society of Clinical Oncology Meeting.* 2013:271-276.

10. Cheung WY. Difficult to swallow: issues affecting optimal adherence to oral anticancer agents. *American Society of Clinical Oncology Educational Book / ASCO American Society of Clinical Oncology Meeting.* 2013:265-270.

11. Geynisman DM, Wong YN. Drug Supply Chain Security Act and Oral Anticancer Medications: Are We Shortchanging Our Patients? *JAMA Oncology.* 2016;2(3):295-296.

12. May P, Figgins B. Oral anticancer therapy: a comprehensive assessment of patient perceptions and challenges. *The Journal of Community and Supportive Oncology.* 2016;14(3):112-116.

13. Dusetzina SB, Huskamp HA, Winn AN, Basch E, Keating NL. Out-of-Pocket and Health Care Spending Changes for Patients Using Orally Administered Anticancer Therapy After Adoption of State Parity Laws. *JAMA oncology.* 2017; 4(6): e173598.

14. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2014;32(4):306-311.

15. Shen C, Chien CR, Geynisman DM, Smieliauskas F, Shih YC. A review of economic impact of targeted oral anticancer medications. *Expert Review of Pharmacoeconomics & Outcomes Research.* 2014;14(1):45-69.

16. Shih YC, Smieliauskas F, Geynisman DM, Kelly RJ, Smith TJ. Trends in the Cost and Use of Targeted Cancer Therapies for the Privately Insured Nonelderly: 2001 to 2011. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2015;33(19):2190-2196.

17. Thanki K, Gangwal RP, Sangamwar AT, Jain S. Oral delivery of anticancer drugs: challenges and opportunities. *Journal of Controlled Release: Official Journal of the Controlled Release Society.* 2013;170(1):15-40.

18. Sikorskii A, Given CW, Given BA, et al. Do treatment patterns alter beliefs cancer patients hold regarding oral oncolytic agents? *Psycho-Oncology.* 2018;27(3):1005-1012.

19. Karnofsky DA. The clinical evaluation of chemotherapeutic agents in cancer. *Evaluation of Chemotherapeutic Agents.* 1949:191-205.

20. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology.* 1982;5(6):649-655.

21. Kaisaeng N, Harpe SE, Carroll NV. Out-of-pocket costs and oral cancer medication discontinuation in the elderly. *Journal of Managed Care & Specialty Pharmacy.* 2014;20(7):669-675.

22. RED BOOK Online. Truven Health Analytics. Retrieved from https://redbook.solutions.aap.org

CHAPTER FOUR: THE IMPACT OF BURDEN OF TREATMENT ON TEMPORARY STOPPAGES OF TREATMENT IN CANCER PATIENTS WITH MULTIMORBID CONDITIONS
(Manuscript Three)

Introduction

It is imperative for oncology providers to understand how the characteristics of an individual can affect their cancer and the associated treatment regimen. Age, sex, body mass index (BMI), race, and an extensive list of other patient characteristics have been extensively researched among cancer patients in order to make oncology providers' decisions on treatment plan easier. However, one patient characteristic that may have a greater influence continues to be a challenge for researchers and clinicians. The presence of multimorbid conditions within cancer patients brings about unique challenges for providers and patients. As the population continues to increase in life expectancy, the issue of cancer and multimorbidity will be an important consideration for researchers and clinicians. For patients, the issue of cancer and multimorbidity brings about an increased number of tasks needed to manage their diseases, as well as distress that accompanies an overwhelming treatment workload.

This combination of a patient workload and their perspective is the *burden of treatment*. The need to examine this concept has become important due to the shift to shorter inpatient stays and a greater emphasis on patient self-management in the home.[1,2] The increase of patient self-management has led to patients being more responsible for their care, and therefore a greater workload, or burden, is imposed upon them. Tran, Sav, and Eton are the three primary contributors to the burden of treatment conceptual literature. Their work began with the conceptualization of burden of treatment and started to empirically measure the concept within certain chronic disease populations.[3-8]

The existing burden of treatment literature has focused on several chronic conditions, including HIV/AIDS,[9-11] mental illness,[15,17] diabetes,[12] cardiovascular diseases,[13] cystic fibrosis,[14] celiac disease,[15] hyperlipidemia,[16] asthma,[4,16] and stroke,[3,16] as well as multimorbidity, or the coexisting of more than one chronic condition.[1] These chronic condition studies have examined

burden of treatment (BOT) through varied designs and variables of interest. Qualitative studies identified themes, such as tasks required of patients to manage their conditions; difficulties with access to care; impact of tasks on self-management; identifying problem solving techniques and coping strategies; importance of social support; and positive aspects of the healthcare system, including positive relationships with providers.[6,16] Some studies reviewed existing literature to examine BOT through conceptual works or by undertaking secondary data analyses. [5,10,11] The quantitative studies utilized indicator variables in order to try and examine BOT as an outcome variable or predictors of patient and clinical consequences. Indicator variables are used in place of the actual variable or concept, due to the fact that it may be more feasible to collect the indicator variable rather than a BOT-specific measurement tool. Examples of the indicator variables included in these studies are treatment complexity,[14,16] number of medications,[11,17] number of interactions with healthcare providers,[18-20] and difficulty managing treatment.[15-17] These indicator variables are components of the workload and perspective components of BOT but are not all the components. Individuals with chronic diseases are required to complete more healthcare tasks than these examples. “Difficultly managing treatment” only provides small insight into the patient perspective of individuals with chronic disease.

While these studies examined BOT across a number of chronic conditions, only three studies were found that examined BOT within cancer patients. Two of these cancer studies analyzed secondary data from large data sets, including the Surveillance Epidemiology and End Results (SEER-Medicare)[18] and an institutional cancer registry.[20] The third study recruited patients from a national survey registry and had direct contact with participants through online surveys and telephone interviews.[19] The three studies examined burden through the following indicator variables: the number of days interacting with the healthcare system,[18-20] type of interaction (i.e. receiving cancer treatment, clinic visit, or ER/acute stay),[18-20] number of physicians patients were interacting with,[18] number of medications,[18] and symptom burden.[19] These studies utilize indicator variables identified within the BOT literature as increasing the

workload of the patient. Although these studies describe the workload imposed upon patients by the healthcare system, the studies do not provide a full picture of cancer patients' burden experience. The studies do not include the patient's perspective of BOT—how this workload increase affects their ability to manage their cancer or the impact on their daily lives.

While these three studies did use indicator variables for BOT, these works have provided valuable insight into the burden imposed upon cancer patients. Looking more specifically at cancer and multimorbidity within these studies, only Presley et al.[18] collected patients' multimorbid conditions and examined the impact on patients' burden. The researchers used the number of days interacting with the healthcare system as an indicator for BOT. What they found across a sample of approximately 8,000 lung cancer patients, when comparing patients that received the same cancer treatment, was those with three or more multimorbidities experienced a significantly higher level of burden than those with less than three multimorbidities. Although this is the only study that specifically examines BOT within cancer patients and measures the impact of multimorbid conditions, other works have illustrated the impact of multimorbidities on a number of cancer patient and healthcare outcomes, including symptoms and side effects, adverse events (e.g. hospitalizations), quality of life, increased costs, disease exacerbation, and mortality.[2,21-25] These works exemplify the struggles that individuals with cancer and multimorbid conditions face on a daily basis, both physically and mentally.[18-20]

Cancer patients that are taking oral oncolytic agents (OOA) experience a different set of challenges when compared to those receiving traditional intravenous (IV) chemotherapy. While trained healthcare professionals manage IV chemotherapy administration in a controlled environment, oral agents lack such firsthand monitoring, thereby shifting treatment responsibility to patients and their families.[26-30] Oral oncolytic agent regimens can be quite complex, comprising multiple oral medications with varying dosages, cycles (days on and days off), and special instructions (e.g., avoid certain medications or food).[29,31] These complex regimens

increase patients' BOT.[32] Because most cancer and multimorbidity management takes place in the home, it is imperative that patients and providers have open communication and providers deliver effective education about side effects, as these can lead to dose modifications, medication interruptions, a switch to IV agents, or a discontinuation of all cancer treatments.

A primary concern for oncology providers are the frequent modifications that take place with oral oncolytic regimens. These modifications may include dose changes; temporary stoppages (i.e. taking some time off from the drug but still continuing with that drug); permanent stoppages (i.e. completely discontinuing that drug); and adding or switching to a new cancer drug.[24,33,34] The regimen modifications can be brought on by side effects and toxicities, interactions with other diseases or medications, patient or provider decisions, or progression of the cancer.[34] Changes in oral oncolytic regimens can alter the effectiveness of the medication, if patients are not receiving a strong enough dose or are taking increased rest periods. Although these changes may affect the plan to cure the cancer or relieve symptoms, regimen modifications may be necessary to keep patients on their oral oncolytics.[26,35]

In addition to the increased complexity and modifications of oral oncolytic medication regimens, patients may also face financial difficulties from paying for oral agents that can cost several thousand dollars per month.[36,37] Difficulties with insurance coverage and the need to use specialty pharmacies can lead to patients discontinuing or delaying necessary cancer treatments.[37-40] Dealing with the problems related to oral oncolytic regimens can create a great deal of stress, making it difficult for cancer patients to continue treatment. Not being able to pay for one's OOA may even cause a patient to have to stop, temporarily or permanently, their oral agent. All of these factors may be multiplied for patients who have other chronic conditions, in addition to cancer, that also require complex management. As patients' workloads increase with additional tasks, these challenges can bring about added stress for patients. With limited research examining BOT, even with indicator variables, among cancer patients with multimorbid conditions, this work will begin to fill that gap.

Purpose

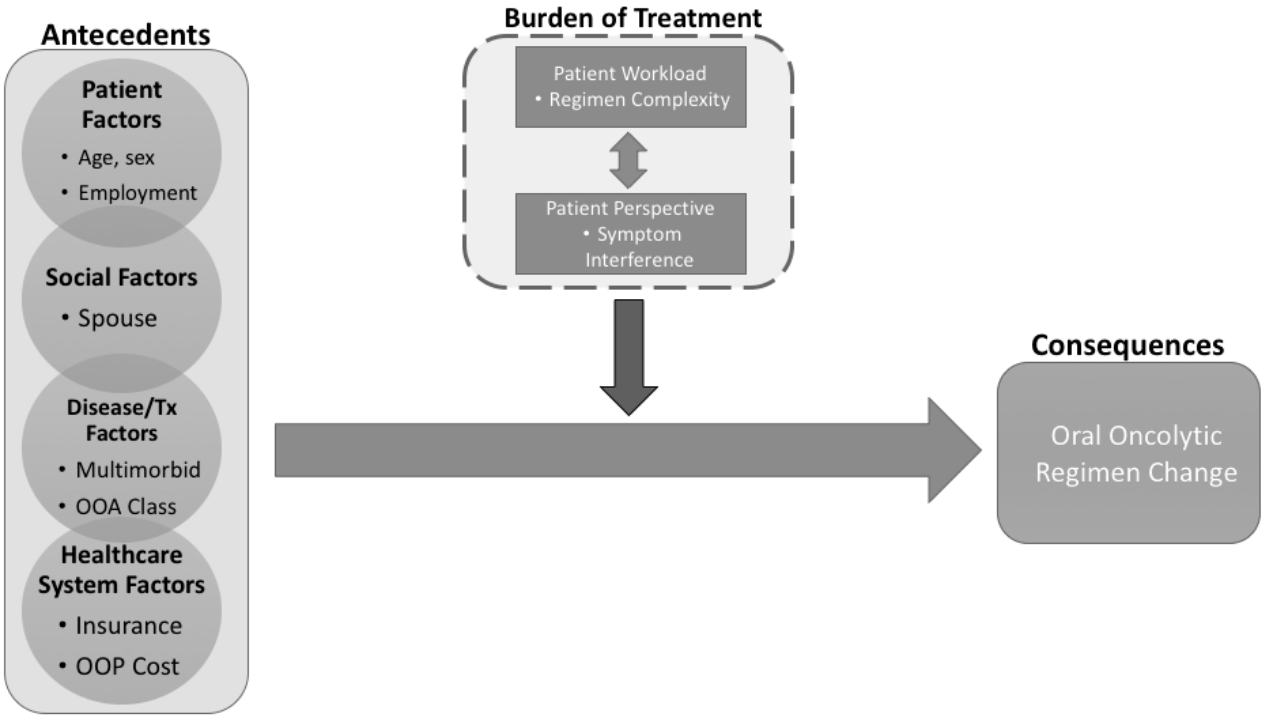
The purpose of this work is to evaluate the moderation effect of BOT indicator variables on the relationship between the baseline characteristics (age, sex, employment status, marital status, multimorbidity, OOA drug class, insurance type, and OOA copay) and continuation of OOA within cancer patients with multimorbid conditions. The following research question will be answered:

- How the burden of treatment indicator variables might moderate the relationship between baseline antecedent factors and the temporary stoppage of patients' oral oncolytic regimens?

Conceptual Model

The Burden of Treatment Morbidity (BOTM) Model will guide the conceptualization of this chapter, as it has for the other chapters within the dissertation. **Figure 4.1** illustrates the an analytical model with similar components to the BOTM Model. Unlike the BOTM, this analytical model shows a moderation relationship. This moderation model focuses on two primary relationships: 1) the direct relationship between the antecedent factors (patient, social, disease/treatment, and healthcare system) and the consequences of the patient and healthcare system; and 2) how BOT, both patient workload and patient perspective, might moderate the strength of the relationship between the baseline antecedent factors and the oral oncolytic regimen change. This chapter will focus on the second relationship. This work will utilize variables from all four of the antecedent factor categories, an indicator variable for both BOT patient workload and BOT patient perspective, and the consequence of treatment regimen changes. The arrow from the antecedent through BOT, and the arrow from BOT to the consequences, illustrates the strength between the antecedents and consequences is impacted by BOT. This analytical model helps the reader visualize the relationships of the variables and the moderation analysis that will examine these relationships.

Figure 4.1. Burden of Treatment Moderation Analysis Model



Methods

This work was a secondary data analysis of a randomized controlled trial (RCT) testing adherence and symptom management interventions in cancer patients that have been newly prescribe OOAs. The parent study, *Improving Adherence to Oral Cancer Agents and Self Care of Symptoms Using an IVR*, funded by the National Cancer Institute (1Ro1CA162401-O1A1), was a two-arm, multisite RCT.[41] The experimental arm received a weekly symptom assessment with referral to a symptom management toolkit for symptoms ≥4/10 and an adherence intervention comprised of daily reminders using an automated interactive voice response (IVR) system. Control patients received standard care without referrals to a toolkit or reminder calls.

Sample

Parent Study Sample. Participants for the parent study were recruited from six NCI-designated comprehensive cancer centers across the Midwest United States. Patients agreed to enroll in

the study by signing a consent form, and could withdrawal at any point during the study. Inclusion criteria for the parent study were as follows: patients were to be 21 years or older; speak English; newly prescribed one of the designated FDA approved oral oncolytics (Appendix A); have an Eastern Cooperative Oncology Group (ECOG) performance of 0–2 or Karnofsky score of ≥50 (Appendix B);[42,43] and actively receiving cancer treatment from one of the participating cancer centers. Exclusion criteria for patients included if they had difficulty hearing on the telephone; limited or no access to a touch-tone phone; cognitive deficits as determined by recruiters; or receiving hospice care.

In the parent study, 482 patients were screened for eligibility, with 438 being eligible, and 322 of these patients consenting for the study. Of the consented patients, 272 patients completed the baseline interview and then randomized into one of the two arms (Appendix C). Institutional review boards (IRB) at the study center and each recruitment site approved the study and all protocols.

Data Collection. Data were collected over the phone by trained interviewers at baseline, 4, 8, and 12 weeks. Interviewers collected information including OOA prescription information and pill counts, demographics, insurance coverage, social support, symptoms, multimorbid conditions, and interactions with healthcare providers. Data were also collected during the experimental group's daily reminder calls, as well as all of the patients' automated weekly, symptom calls. After patients completed the study, trained abstractors at the respective cancer centers completed medical record audits (MRA) (Appendix D). Every MRA received quality assurance checks, as well as randomly selected interviews each month for all patient interviewers.

Secondary Data Sample. All 272 participants that completed the baseline interview will be included in this secondary data analysis. Participants are not differentiated by experimental/control groups as the interventions had no impact over and beyond usual care.

Measures

Table 4.1. summarizes the constructs, measures, and descriptions from the parent study utilized in this secondary analysis. Patient sociodemographics include age, sex, marital status, and employment status (Appendix E). Healthcare system antecedents include the type of insurance and presence of an out of pocket (OOP) cost for the oral oncolytic at baseline. Oral oncolytic drug class and multimorbidities requiring medication management are used for disease/treatment antecedents. These multimorbidities were based on pre-existing (before the study period) prescriptions for medications primarily used to treat the specific conditions, found in the medical record. Two nurses on the research team reviewed the multimorbid conditions and medications.

Table 4.1. Secondary Data Analysis BOT Moderation Variables

Construct	Measures	Description
Patient Characteristics	Age, Sex, Employment Status, Marital Status,	Patient reported during screening and baseline interview Age (continuous); Sex (male, female); Employment Status (employed, unemployed); marital status (married, divorced/widowed, never married)
	Multimorbid Conditions	Pre- existing prescriptions reported in MRA used for management of conditions. Multimorbidities will be analyzed as a continuous variable
Cancer Characteristics	Treatment Protocol	Class of the oral oncolytic (cytotoxic, kinase inhibitor, sex hormone inhibitor, and other)
Healthcare System	Insurance Type	2 categories: government and private/commercial
	Oral Oncolytic Out of Pocket (OOP) Cost	Yes/No. Patient had OOP cost for their oral oncolytic at baseline
Burden of Treatment	Medication Regimen Complexity Index (MRCI)[31]	Weighted algorithm of 19 variables in order to capture the complexity of the oral oncolytic protocol
	Cancer Symptom Experience Inventory (CSEI) – Interference Scale	Patient reported. Summed score of 19 variables with scale from 0-9 on the interference on daily activities (range 0-162)
Outcome Variable	Temporary Stoppage	Whether or not patient experienced temporary stoppage of their OOA regimen

Burden of treatment indicator moderation variables are being used for both patient workload and patient perspective. Patient workload was captured through oral oncolytic regimen complexity scores, which were measured using an adapted version of George's et al.

Medication Regimen Complexity Index (MRCI).[44] George et al. created the complexity index in order to capture the complexity of a patient's medication regimen, including times per day, having to crush or dissolve pills, having to take with specific food or liquid, and taking multiple pills per dose. The pharmacy team designated weights for specific variables, with larger weights designated variables that add more complexity to the medication regimen. George and colleagues worked through multiple levels of measurement testing in order to ensure the most valid and reliable tool. Expert panels tested actual patient medication regimens, who had a primary diagnosis of chronic obstructive pulmonary disease (COPD) but also taking medications for other conditions. Six different levels of evaluation took place involving the authors, pharmacists, a research nurse, an adherence expert, a pharmacy academic, and a home-medication-review consultant. Each step included different evaluations, such as content validity, inter-rater reliability, test-retest reliability, and discussions to modify the tool for user feasibility, proper weightings, and completeness of included variables. Kendall's coefficient of concordance was used to correlate the agreement on patient medication regimens between five experts. Spearman's Rho was used to determine correlation between the experts and the MRCI. Significant agreement was found between the expert panel and the new MRCI tool when ranking the patient medication regimens

The parent trial study applied 18 specific variables of the MRCI to the patients' regimens in order to capture the complexity of their oncolytic regimen. The others variables did not apply to oral oncolytic regimens and were excluded. The only other added variables were each 1-point weighted variables and were for the number of injections and IV chemotherapies in patients' baseline treatment protocols. **Table 4.2.** shows all of the included variables from the MRCI with a scoring example for a possible patient regimen. Below is a detailed example.

A breast cancer patient prescribed Xeloda (capecitabine) is also receiving platinum-based IV chemotherapy and a monthly adjuvant hormonal injection. The Xeloda is 500mg tabs with four pills in the morning and three pills in the evening, cycling the medication two weeks on

and one week off. The number of oral oncolytic medications that fit the variable criteria is added to that box. For this patient, the number of variables that match the Xeloda regimen is "1." Patients on multiple medications might have a two or more if multiple medications matched the variable criteria. After entering the total number of medications that match each variable, these numbers are multiplied by the variable weighting. The weighted variable scores are added together for a final patient complexity score. This example patient will result in a complexity score of 12.

Table 4.2. Medication Regimen Complexity Index (MRCI) Adaptation Description

Variable	Description	Weighting of Variable	Patient Example	Weighted Patient Example
1. Patient ID	Patient ID	N/A		
2. Start Date	Date for which the oral agent chemotherapy (OA) protocol began	N/A		
3. End Date	Date for which the OA protocol stopped or changed	N/A		
4. Capsule/Tablets	Number of all individual oral medications in OA Protocol	1	1	1
5. Once Daily	Medication taken once per day	1	0	0
6. Once Daily PRN	Medication taken once per day as needed	0.5	0	0
7. Twice Daily	Medication taken twice per day	2	1	2
8. Twice Daily PRN	Medication taken twice per day as needed	1	0	0
9. Three Times Daily	Medication taken three times per day	3	0	0
10. Three Times Daily PRN	Medication taken three times per day as needed	1.5	0	0
11. Cycling	If medication is not taken every day, but instead a cycle format. There will be certain days to take the medication and certain days to not	2	1	2
12. Break or Crush	Medication must be broken or crushed before administering	1	0	0
13. Dissolve	Medication must be dissolved in liquid, usually water, before administering	1	0	0
14. Multiple Pills per Dose	More than one pill to be taken with each dose	1	1	1
15. Variable Dose	Not a specific number of pills per dose, but for example could be 2-3 pills per dose	1	1	1
16. Take at a Specific Time	Medication must be administered at a specific time of the time (e.g. 9 a.m. and 7 p.m.)	1	0	0
17. Relation to Food	Specific directions, such as to be taken on an empty stomach or with food	1	1	1

Table 4.2. (cont'd)

Variable	Description	Weighting of Variable	Patient Example	Weighted Patient Example
18. Take with Specific Liquid	Specific directions in relation to liquid, such as take with a full glass of water or drink 2L per day	1	0	0
19.Tapering/Increasing Dose	If the original prescription starts at a specific dose and then after a certain amount of time (i.e. 2 weeks) increase or decrease the dosage by a specified amount	2	0	0
20. Alternating Dose	Different doses during the day (e.g. take 2 pills in the morning and 3 pills at night)	2	1	2
21. Injection Therapy	Point for each injection therapy on the OA protocol	1	1	1
22. Intravenous (IV) Therapy	Point for each IV therapy on the OA protocol	1	1	1
23. Complexity Score	Summed score of variables 4-22, with weighting taken into account	N/A		12

Adapted Version of George et al. Medication Regimen Complexity Index (MRCI). Weighting was determined by the George's team. Only the above variables were selected, as they apply to oral oncolytics, while the others did not. An algorithm was created by this researcher to multiply the number of medications in each filed by its respective weight, and then add each variable to equal the complexity score.

The indicator BOT-patient perspective variable is patient baseline-symptom interference. Cancer Symptom Experience Inventory (CSEI) measured symptom interference, which contains reports on 18 symptoms commonly associated with oral oncolytic therapy (Appendix F).[45] Patients were asked if they have had each symptom in the last seven days due to cancer or its treatment. If they said "yes," patients rated the symptom severity at its worst on a 1–9 scale (1 = very little; 9 = worst possible) and rated overall interference in daily activities over the last seven days on a scale from 0–9 (0 = did not interfere; 9 = interfered completely). Interference is associated with patient perspective of the burden brought on by their cancer and the treatment. The "0–9" interference scores for each of the 18 symptoms will be summed, with a higher score meaning greater interference from the cancer or its treatment on the patient's daily activities (range 0–162). Symptom interference was included over symptom severity, because it better captures patients' perspective of how symptoms impact their lives.

The outcome variable is a binary variable of whether or not patients experienced a temporary stoppage of their OOA regimen over the course of the parent trial (12 weeks). Oral oncolytic agent regimens may require a number of changes, including dose changes, temporary stoppages, and permanent stoppages. Patients have more of a chance to influence temporary stoppages than permanent stoppages, either through effective management of symptoms and side effects or decisions made by themselves or their oncologist. Temporary stoppages are often accompanied by dose reductions, and dose reductions are often less burdensome to patients. Permanent stoppages are most often due to disease progression and therefore, have little to no patient input.

Data Analysis

Data were analyzed using STATA/IC 14.0 Software. Descriptive statistics and frequencies were used to measure patient and cancer characteristics and the frequency of temporary cancer treatment regimen stoppages. Effect coding was used for the categorical predictor variables within the models, coded as (1, -1). In order to standardize continuous variables, the group means for regimen complexity, symptom interference, and number of multimorbid conditions were subtracted from each individuals' value.

For the primary research question, a moderation analysis was implemented using two multiple logistic regression models, based on Baron and Kenny and MacKinnon.[46] The outcome for both models was whether an individual experienced a temporary stoppage during the 12-week parent trial. Because the primary focus for this dissertation is the burden of cancer patients with multimorbid conditions, patient multimorbidities will be the antecedent variable included in the interaction term with the BOT indicator variables (regimen complexity and symptom interference). Chi-square tests and simple logistic regressions were completed for categorical and continuous variables, respectively, to test the main effect of each predictor on the outcome of temporary stoppages. Significant main effects and the moderation variables were included in the final regression models. If the moderation interaction terms were found to

be non-significant, then a main effects regression model including the significant main effects and three moderation variables (multimorbidity, regimen complexity, and symptom interference) would be analyzed.

Results

The secondary analysis sample included all 272 participants from the parent trial that completed the baseline interview. The sample was evenly split between males and females and had a mean age of 61 years (**Table 4.3.**). Approximately one third of the sample was employed, either part time or full time, and 61% were married at the time of their intake interview. More than half of patients' (57%) primary insurance was government coverage, which included Medicare, Medicaid, and Veterans Affairs (VA). For their initial OOA prescription, 53% had an OOP cost, with a mean cost of $258 (USD). Of the 28 different main oral agents prescribed to patients, 82% were either in the cytotoxic or kinase inhibitor drug-classes. In addition to being prescribed an OOA, 27% of the trial sample were also receiving IV chemotherapy at baseline. **Table 4.4.** displays the sex differences of the continuous predictor variables, with females having a significantly higher mean symptom interference score (*P* 0.039).

Table 4.5. displays the correlations between the continuous predictor variables. Age was significantly correlated with multimorbid conditions ($P < .01$) and symptom interference ($P = .01$). The number of multimorbid conditions increased with age. The opposite was true for symptom interference; as age decreased, symptom interference increased. Both of these relationship are well documented Both of these relationship are well documented within literature. As individuals age they have a greater likelihood to be diagnosed with chronic conditions.[2] Younger cancer patients often have a more aggressive disease status, therefore, having a higher symptom burden.[47]

In addition to their cancer, patients had, on average, 3.39 chronic conditions requiring medication management, with an average of 12 non-cancer treatment medications per patient. The most common multimorbidities were cardiovascular disease, peptic ulcer disease,

depression, diabetes, hyperlipidemia, and renal disease. A patient's average treatment-regimen complexity score was 6.8 (range: 1–16). Patients had an average baseline symptom-interference score of 17.8 (range: 0–119). Over the course of the 12-week parent trial, 99 patients (36%) experienced at least one temporary stoppage of their cancer treatment regimen. **Table 4.6.** shows the frequency of temporary interruptions by the baseline categorical variables.

In building the final moderation regression models, chi-square tests showed sex and OOA drug-class had significant group differences in terms of temporary stoppages. Females were more likely to experience a temporary stoppage over the course of the trial ($P < 0.001$). After testing OOA drug-class using logistic regression with effect coding, those prescribed cytotoxics ($P = 0.049$) and kinase inhibitors ($P = 0.004$) experience a greater number of temporary stoppages than those taking sex hormone inhibitors and other OOAs. Age, marital status, employment status, type of insurance, and whether or not patients had an OOP cost for their first OOA prescription showed no significant differences in terms of temporary stoppages, and thus were not included in the final moderation regression models. Given that age was non-significant, the issue of multicollinearity with multimorbid conditions and symptom interference is not a problem moving forward with the multiple regression models.

Table 4.7. shows the results for the first moderation regression model that included the interaction term of multimorbidity and cancer treatment-regimen complexity (patient workload). Similar to the individual model building tests, both sex and OOA drug class had significant effects on temporary stoppages. However, when including all of the predictor variables in the model, cytotoxics no longer had a significant effect. Females (P 0.018) and those prescribed kinase inhibitors (P 0.003) were more likely to experience temporary stoppages. Neither the main effects of multimorbidity and treatment regimen complexity, nor the interaction term between the two variables had a significant impact on temporary stoppages over the course of 12 weeks. However, cytotoxic agents no longer has a significant impact.

Table 4.8. shows the results for the moderation regression models that include the interaction between multimorbidity and baseline symptom interference (patient perspective). This model had similar results to the previous model that included multimorbidity and regimen complexity. Females (P = 0.008) and those prescribed kinase inhibitors (P = 0.01) were more likely to experience a temporary stoppage over the course of the trial. Neither the main effects of multimorbidity and symptom interference, nor the interaction between multimorbidity and symptom interference had a significant impact on temporary stoppages of a patient's cancer treatment regimen. As was the case in patient workload X multimorbidity model, cytotoxic agents no longer had a significant impact.

Both of the interaction terms between symptom interference and multimorbidity and OOA regimen complexity and multimorbidity were non-significant within their respective models. Therefore, a regression model was conducted that included sex, OOA drug class, symptom interference, regimen complexity, and multimorbidity (**Table 4.9.**). Much like the interaction terms, the main effects for the BOT variables were non-significant. However, like the moderation models, sex and OOA drug class were significant. Females (P=0.018) and patients prescribed kinase inhibitors (P=0.004) were more likely to experience a temporary stoppage during the parent trial. Much like the moderation models, cytotoxic agents no longer had a significant impact.

Discussion

Individuals with cancer are continuing to live longer as cancer treatments have become more effective. Consequently, this longer survival time increases the chances that an individual with cancer will have other chronic conditions that require medical management. With the population of individuals with cancer and multimorbid conditions rising, it is important to understand the BOT these individuals face while managing their cancer and multimorbid conditions.[2,22] This work is the first study that could be found to examine the BOT of individuals prescribed OOAs

that have to medically manage other multimorbid conditions. Similar to previous cancer BOT studies,[18-20] this work used indicator variables instead of a BOT-specific measure in order to measure BOT components. However, unlike these three previous studies, this analysis included an indicator variable for patient perspective (patient reported symptom interference) as well as an indicator variable for patient workload (cancer treatment regimen complexity).

Oral oncolytic agents are a last line of treatment for most cancer patients, and patients could theoretically be taking them until the end of life.[21,48] Symptom burden is a primary concern for oncology providers in the management of OOAs. Increased symptom burden is one of the main reasons for patients needing temporary stoppages or dose changes with their OOA regimens. Symptoms were the most common reason for temporary stoppages in the parent trial. Of the 99 participants that experienced a temporary stoppage, the most common symptoms and toxicities associated with temporary stoppages were fatigue, anemia, abnormal blood counts, cold/flu-like symptoms, nausea/vomiting, skin rash, and hand-foot syndrome. Additionally, about 25% of the sample experienced a permanent stoppage of their treatment regimen. Permanent stoppages are primarily driven by disease progression, and are therefore not as influenced by the patient like temporary stoppages.[49]

The results of the initial group difference analysis indicate females and those prescribed kinase inhibitors and cytotoxic agents were more likely to experience a temporary stoppage of their cancer treatment regimen. The two moderation regression models showed similar results. However, when factoring in sex, multimorbidity, treatment regimen complexity, and baseline symptom interference, cytotoxic agents no longer had a significant difference in terms of temporary stoppages. Given the different symptom profiles associated with certain OOAs, differences in temporary stoppages among OOA drug classes was expected.[50,51] The most commonly prescribed kinase inhibitors in the parent trial were palbociclib, pazopanib, sorafenib, and regorafenib.

To explore the significant impact of sex on temporary interruption, an additional analysis was completed examining the differences between males and females. Although females had a significantly higher mean symptom interference score at baseline (P = 0.038), there was no difference between males and females after taking their OOAs for four weeks. With symptoms being the primary driver behind temporary stoppages, it is unclear why females experienced a significantly higher number of temporary interruptions than males in the parent trial. This could possibly be related to females having a slightly higher average OOA complexity regimen score and more multimorbid conditions than males. It could also be related to females taking OOAs that had higher proportions of temporary stoppages. Future research will be needed to examine sex differences related to OOA regimen modifications.

The results of the moderation regression analyses showed no significant impact on temporary stoppages within the two models resulting from the main effects of cancer treatment-regimen complexity (patient workload), baseline symptom interference (patient perspective), or multimorbidity and the significant interaction effect. This was not an expected finding as recent literature has described the impact of multimorbidities on the management of cancer treatment and overall quality of life of cancer patients.[2,22,52-54] Although multimorbidity was non-significant, there was a descriptive trend of increased multimorbid conditions being associated with a larger proportion of temporary stoppages. The reason for lack of significant findings could be related to the measurement of multimorbidities, which was operationalized based on non-cancer prescription medications within patients' MRA. The same could be said for the use of BOT-indicator variables as opposed to a BOT-specific measure. Although not statistically significant, individuals with multimorbid conditions had a higher frequency of temporary stoppages than patients with no multimorbidities. Given this, more research is needed examining the impact of multimorbid conditions on the treatment outcomes of patients prescribed OOAs.

Limitations

Utilizing indicator variables for the BOT components was a limitation of this secondary analysis. Utilizing other measures for patient workload and perspective, such as a validated BOT scale, may have yielded different results within the study sample. Inclusion of ICD-10 diagnoses within the parent trial may have improved the measurement of multimorbidities. The sample lacked racial diversity and was highly educated, and thus was not representative of the U.S. population. Finally, the follow-up period of the parent trial was 12 weeks. A longer follow-up time may have shown different results as patients' cancer treatments progress.

Conclusions

In the secondary analysis, we found that more than a third of patients experienced a temporary stoppage in their cancer treatment regimen over the course of 12 weeks. With a short observation period, this shows the volatility of cancer treatment for those prescribed OOAs. Females and patients prescribed kinase inhibitors were more likely to experience temporary stoppages than males and patients prescribed other OOA class, respectively. These patients are often in a difficult period of their cancer care trajectory, as the majority of solid tumor cancer patients have gone through several lines of treatment before being prescribed OOAs. If these patients medically manage other chronic conditions as well, the complexity of management and level of burden may be increased. This work begins to highlight the importance of examining factors that may affect patients' OOA regimens. Although multimorbidity did not prove to have a significant impact within this sample, the impact of multimorbid conditions on the care and quality of life of cancer patients needs further research. As the population lives longer, individuals with cancer and other multimorbid conditions will become a norm. Continued research efforts within this population will be vital for practice guidelines and empowering patients to self-manage their OOAs and other multimorbid conditions in the home effectively.

Table 4.3. Descriptive Statistics for the Secondary Analysis Study Sample (N=272)

Characteristic	**n (%)**
Sex	
Male	136 (50)
Female	136 (50)
Race	
African American	22 (8)
Caucasian	241 (89)
Other/unknown	7 (3)
Level of education	
High school or less	71 (26)
Some college or completed college	150 (55)
Graduate or professional degree	49 (18)
Unknown	2 (1)
Employment status	
Employed	88 (32)
Unemployed	184 (68)
Marital status	
Married	167 (61)
Not married	105 (39)
Insurance type	
Government	154 (57)
Private/Commercial	118 (43)
Oral agent copay	
Yes	143 (53)
No	114 (42)
Don't know	15 (5)
Drug category	
Cytotoxic agents	95 (35)
Kinase inhibitors	127 (47)
Sex hormone inhibitors	27 (10)
Other	23 (8)
IV Chemotherapy at Baseline	
Yes	73 (27)
No	199 (73)
Temporary Treatment Interruption	
Yes	99 (36)
No	173 (64)

Table 4.4. Sex Differences of Predictor Variables (N=272)

Characteristic	Male Mean (SD)	Female Mean (SD)	Total Mean (SD)
Age (years)	63.10 (12.34)	59.67 (11.89)	61.38 (12.22)
Multimorbid Conditions	3.22 (2.04)	3.55 (1.93)	3.39 (1.99)
Cancer Treatment Regimen Complexity	6.67 (2.71)	6.95 (2.62)	6.81 (2.67)
Baseline Symptom Interference	15.33 (20.36)	20.35 (19.55)	17.84 (20.08)

Table 4.5. Correlations of Continuous Predictor Variables

	Age	Multi	SI	CRC
Age	1.0000			
Multi	0.1825*	1.000		
SI	-0.1548*	0.0086	1.000	
CRC	-0.0457	-0.0145	0.011	1.000

Abbreviations: Multi, multimorbidity; SI, symptom interference; CRC, cancer regimen complexity
*Statistically significant correlation

Table 4.6. Frequency of Temporary Interruptions by Baseline Antecedent Factors (N=272)

	Temporary Interruption		
Baseline Characteristic	Yes n (%)	No n (%)	Total
Sex			
Male	34 (25%)	102 (75%)	136
Female	65 (48%)	71 (52%)	136
Age			
<65 Years Old	57 (36%)	100 (64%)	157
65+ Years Old	42 (37%)	73 (63%)	115
Marital Status			
Married	60 (36%)	107 (64%)	167
Not Married	39 (37%)	66 (63%)	105
Employment Status			
Employed	33 (38%)	55 (62%)	88
Not Employed	66 (36%)	118 (64%)	184
No. of Multimorbidities			
0	4 (19%)	17 (81%)	21
1-3	46 (36%)	81 (64%)	127
4+	49 (40%)	75 (60%)	124
Drug Class			
Cytotoxic	35 (37%)	60 (63%)	95
Kinase Inhibitors	55 (43%)	72 (57%)	127
Others	8 (35%)	15 (65%)	23
Sex Hormone Inhibitors	1 (4%)	26 (96%)	27
Insurance Type			
Government	61 (40%)	93 (60%)	154
Private	38 (32%)	80 (68%)	118
OOA Copay			
Yes	51 (36%)	92 (64%)	143
No	41 (36%)	73 (64%)	114
Not sure	7 (47%)	8 (53%)	15
Total	99 (36%)	173 (64%)	272

Table 4.7. Multimorbidity x Regimen Complexity Moderation Effect on Temporary Stoppages

	B (SE)	*OR*	*p-value*
Sex			
Male	-0.332 (0.14)	0.717	0.018
Female (ref)			
Drug Class			
Cytotoxic	0.563 (0.34)	1.755	0.095
Kinase Inhibitors	1.053 (0.35)	2.867	0.003
Others	0.549 (0.45)	1.731	0.220
Sex Hormone Inhibitors (ref)			
Multimorbidity	0.049 (0.07)	1.051	0.472
Regimen Complexity	0.094 (0.06)	1.099	0.118
Multimorbidity x Regimen Complexity	0.044 (0.03)	1.045	0.117

Abbreviations: SE, standard error; OR, odds ratio; ref, referent

Table 4.8. Multimorbidity x Symptom Interference Moderation Effect on Temporary Stoppages

	B (SE)	*OR*	*p-value*
Sex			
Male	-0.366 (0.14)	0.694	0.008
Female (ref)			
Drug Class			
Cytotoxic	0.557 (0.33)	1.746	0.090
Kinase Inhibitors	0.811 (0.32)	2.250	0.010
Others	0.375 (0.43)	1.455	0.384
Sex Hormone Inhibitors (ref)			
Multimorbidity	0.027 (0.07)	1.027	0.690
Symptom Interference	0.002 (0.01)	1.003	0.658
Multimorbidity x Symptom Interference	0.001 (0.00)	1.001	0.824

Abbreviations: SE, standard error; OR, odds ratio; ref, referent

Table 4.9. Predictor Variable Main Effects on Temporary Stoppages

	B (SE)	*OR*	*p-value*
Sex			
Male	-0.329 (0.14)	0.719	0.018
Female (ref)			
Drug Class			
Cytotoxic	0.495 (0.33)	1.641	0.135
Kinase Inhibitors	0.980 (0.34)	2.667	0.004
Others	0.456 (0.44)	1.578	0.296
Sex Hormone Inhibitors (ref)			
Multimorbidity	0.035 (0.07)	1.036	0.604
Symptom Interference	0.003 (0.01)	1.003	0.695
Regimen Complexity	0.090 (0.06)	1.094	0.125

Abbreviations: SE, standard error; OR, odds ratio; ref, referent

APPENDICES

APPENDIX A: FDA Approved Oral Oncolytic Agents Included in the Parent Study

Table 4.10. FDA Approved Oral Oncolytic Agents Included in the Parent Study

Oral Oncolytic Agents Organized Alphabetically by Trade Name	
Afinitor (Everolimus)	Stivarga (Regorafenib)
Bosulif (Bosutinib)	Sutent (Sunitinib)
Gilotrif (Afatinib)	Tafinlar (Dabrafenib)
Gleevec (Imatinib)	Tarceva (Erlotinib)
Ibrance (Palbociclib)	Tasigna (Nilotinib)
Imbruvica (Ibrutinib)	Temodar (Temozolomide)
Inlyta (Axitinib)	Tykerb (Lapatinib)
Lenvima (Lenvatinib)	Votrient (Pazopanib)
Lonsurf (Tipiracil & Trifluridine)	Xalkori (Crizotinib)
Lynparza (Olaparib)	Xeloda (Capecitabine)
Nexavar (Sorafenib)	Xtandi (Enzalutamide)
Pomalyst (Pomalidomide)	Zydelig (Idelalisib)
Revlimid (Lenalidomide)	Zykadia (Ceritinib)
Sprycel (Dasatinib)	Zytiga (Abiraterone acetate)

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX B: Eastern Cooperative Oncology Group Scale of Performance Status & Karnofsky Status Performance Scale

Table 4.11. Eastern Cooperative Oncology Group Scale of Performance Status & Karnofsky Status Performance Scale

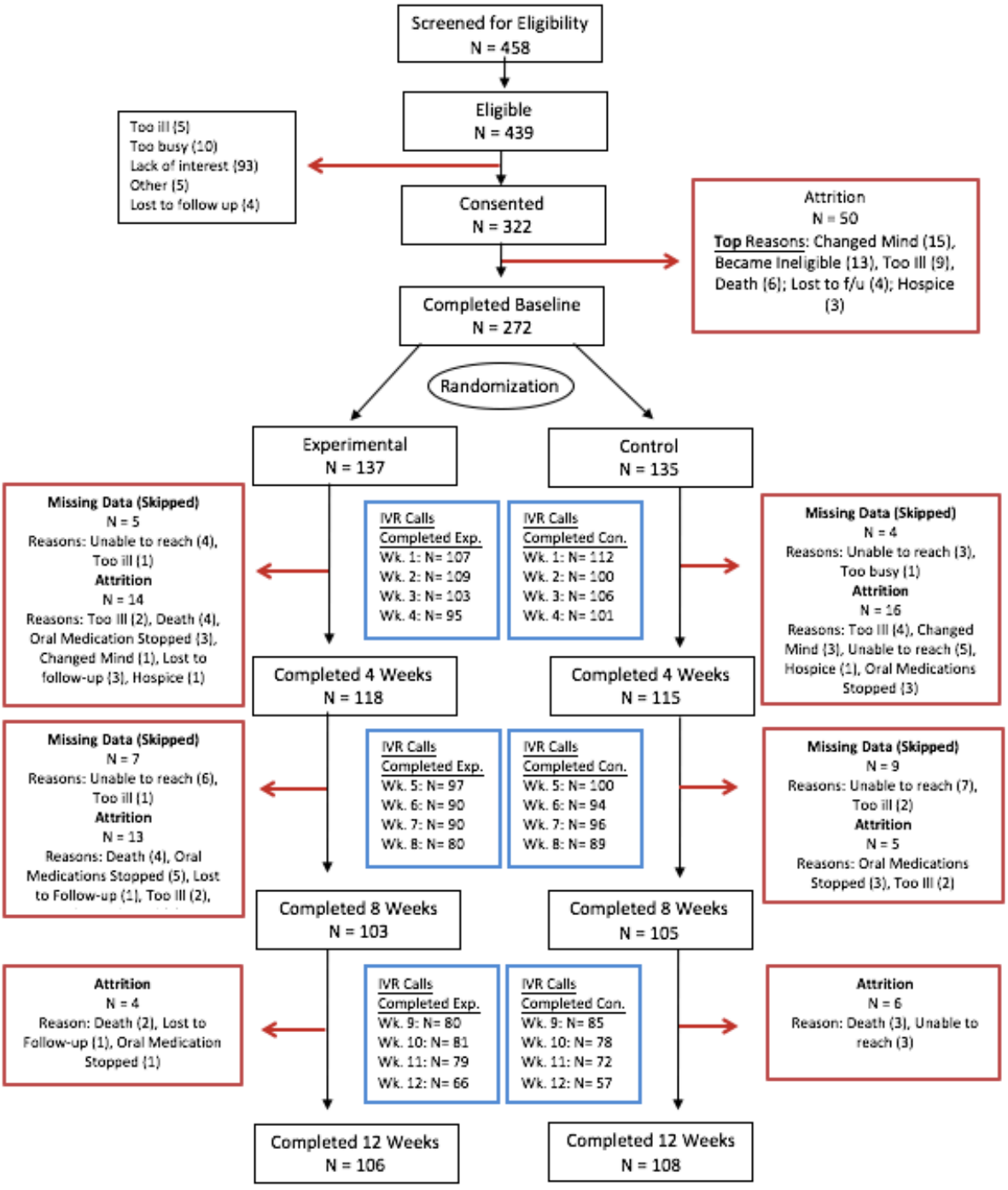
WHO/ECOG Grade	WHO/ECOG Activity	Karnofsky Grade	Karnofsky Activity
0	Fully active, able to carry on all normal activities without restriction	100%	Normal no complaints; no evidence of disease
		90%	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80%	Normal activity with effort; some sign or symptoms of disease
		70%	Cares for self; unable to carry on normal activity or do active work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60%	Requires occasional assistance, but is able to care for most personal needs
		50%	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40%	Disabled; requires special care and assistance
		30%	Severely disabled; hospitalization admission is indicated, although death not imminent
4	Completely disabled. Cannot carry on any self-care, totally confined to bed or chair.	20%	Very sick; hospital admission necessary; active support treatment is necessary
		10%	Moribund; fatal processes progressing rapidly
5	Dead	0%	Dead

Karnofsky DA. The clinical evaluation of chemotherapeutic agents in cancer. *Evaluation of Chemotherapeutic Agents.* 1949:191-205.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology.* 1982;5(6):649-655.

APPENDIX C: Parent Study CONSORT Flow Chart

Figure 4.2. Parent Study CONSORT Flow Chart



Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX D: Parent Study Medical Record Audit

BACKGROUND

Patient Initials: _____ **Gender:** □ Male □ Female

Audit Start Date __/__/__/____(mm/dd/yyyy) ***(1 month prior to consent date)*** **Audit End Date** ___/____/____(mm/dd/yyyy) ***(12 week interview date)***

Date of Audit: _____ **Abstractors Initial:** _____

Notes of special alerts for searching medical record for this patient e.g., patient reported surgeries or hospitalizations during the audit period:

Performance Site (*check one*):

□ Breslin □ Indiana University □ Northwestern □ Ohio State University
□ Sparrow □ University of Michigan □ University of Pittsburgh □ Yale
□ _____(other)

Date of initial diagnosis for the cancer being treated (mm/dd/yyyy) _____

Patient Height _____(in) **Patient Weight** _____(lbs) **Date of Height/Weight**_____

If patient died during the study, date of death (mm/dd/yyyy) ____

Site of Current Cancer Diagnosis (*check one, if more than one diagnosis, check site being treated with an oral agent*):

□ Breast □ Colon/Rectal □ Small Cell Lung □ Pancreas □ Lymphoma
□ Prostate □ Gastrointestinal □ Kidney □ Leukemia □ Non Small Cell Lung
□ Unknown □ Other (*write in*) _____

If there is a second primary cancer (non metastasized) (*check one*):

□ Breast □ Colon/Rectal □ Small Cell Lung □ Pancreas □ Lymphoma
□ Prostate □ Gastrointestinal □ Kidney □ Leukemia □ Non Small Cell Lung
□ Unknown □ Other (*write in*) _____

Stage of Disease (*check one*): □ I □ II □ III □ IV □ Not Staged

Stage of Disease at study start: □ I □ II □ III □ IV □ Not Staged

For Small Cell Lung only: □ Limited □ Advanced

TNM stage (*fill in number*): T _____ N _____ M _____

If unable to record TNM, check one below:
□ Localized □ Metastatic

Additional Information (i.e., grade, etc.): Grade (*write in*) _____

Record location of metastasis (*check all that apply*): □ Brain □ Lung □ Bone □ Liver
□ Other (*write in*) _____

Is this diagnosis a recurrent disease (*disease free \ remission period*)? (*check one*)
□ Yes □ No □ Don't know

Did progression of the disease occur during this audit period? □ Yes □ No □ Don't know

Was the patient undergoing treatment during the month prior to starting on Oral Agents? □ Yes
□ No

Did the patient receive **infusion chemotherapy** in the audit period? □ Yes □ No □ Don't know

If yes, when did he/she **START infusion chemotherapy**? ___/___/____(mm/dd/yyyy)
(write in) If yes, when did he/she **END infusion chemotherapy**? *(write in)* (*NOTE leave END date blank if ongoing*) ___/___/____(mm/dd/yyyy)

Infusion chemotherapy drug name(s): *(write in)*_____

If stopped, reason stopped **infusion chemo**? □ Side Effect □ Complication □ Completed

Has patient received **radiation** in the audit period? □ Yes □ No □ Don't know

If yes, when did he/she **START radiation**? ____/____/_____(mm/dd/yyyy)
(write in) If yes, when did he/she **END radiation**? *(write in)* (*NOTE leave END date blank if ongoing*) ____/____/_____(mm/dd/yyyy

If stopped, reason stopped **radiation**? □ Side Effect □ Complication □ Completed

Did patient have **surgery** since starting oral agent? □ Yes □ No □ Don't know

If yes:
Date of surgery *(write in)* __/____(mm/yyyy) Procedure(s) *(write in)* _____
Date of surgery *(write in)* __/____(mm/yyyy) Procedure(s) *(write in)* _____

Patient visits to **Oncology clinic** during audit period:

Date ____/____/_____ (mm/dd/yyyy)	Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy)	Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy)	Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy)	Reason for visit _____ *(write)*
Date ____/____/_____ (mm/dd/yyyy)	Reason for visit _____ *(write)*

Patient **hospitalized** during audit period:

Date Admitted ___/___/___(mm/dd/yyyy) Date Discharged___/___/___(mm/dd/yyyy)
Date Admitted ___/___/___(mm/dd/yyyy) Date Discharged___/___/___(mm/dd/yyyy)
Date Admitted ___/___/___(mm/dd/yyyy) Date Discharged___/___/___(mm/dd/yyyy)

Patient visits to **ER / Urgent Care** during audit period:

Date ___/___/_____(mm/dd/yyyy) Reason for visit _____*(write in)*
Date ___/___/_____(mm/dd/yyyy) Reason for visit _____*(write in)*

Is there evidence of **screening for mutations prior** to starting oral agent? □ Yes □ No □ Don't know

If yes, check the appropriate box:

□ ALK (Lung)
□ BCR-ABL (T3151)
□ BRAF (Melanoma)
□ BRCA 1 or 2
□ DPYD
□ EGFR (Breast, Colon, Lung)
□ FISH
□ HER2 + or -
□ KIT
□ KRAS (Colon)
□ PDGFR
□ Ph+ Chromosome
□ TSCI1 or 2
□ V600E/K
□ Other mutation *(write in)*_____
□ Other mutation *(write in)*_____

Where did the patient get their oral agent?

Hospital pharmacy □ Yes □ No □ Don't
Local pharmacy (CVS, Walgreen, etc.) □ Yes □ No □ Don't
Specialty Pharmacy □ Yes □ No □ Don't

Table 1: Cancer Protocols and Drugs during Audit Period: PROTOCOL 1

Name of Drug(s) in Protocol 1 (Injection, Infusion, Patch)	Date Prescribed	Dose or Injection (mg per pill or mg/ml)	No. Pills/Day or Injections, Infusions or Patches	Continuous Dosing	Start on Cycle Day	No. of Days On in a Cycle	Number of Days Off in a Cycle	Drug Ongoing	Discontinuation Permanent (P) or Temporary (T) & Date(s)	If stopped (changed), Why? (choose Reason Number below)
Drug 1 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 1	__/__/__			**Yes / No**				**Yes / No**		
Drug 2 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 2	__/__/__			**Yes / No**				**Yes / No**		
Drug 3 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 3	/ /			**Yes / No**				**Yes / No**		

Use this table to determine the **Reason Number** to complete the final column 'If Stopped, changed or discontinued...' above. Write in all that apply

#	Reason	#	Reason	#	Reason - Delay of Drugs / Stoppage
1	Anemia	12	Dyspnea (Shortness of Breath)	23	Peripheral Neuropathy
2	Anorexia	13	Edema, Limb	24	Pruritus / Skin Problem / Rash
3	Arthralgias/Myalgias	14	Fatigue (Asthenia, Lethargy, Malaise)	25	Pulmonary problems
4	Bleeding/Hemorrhage	15	Febrile Neutropenia	26	Renal Failure
5	Cardiac Problems	16	Fever without Neutropenia	27	Thrombocytopenia (low platelets)
6	Completed prescribed protocol	17	Insomnia (Difficulty Sleeping)	28	Protocol completed
7	Constipation	18	Mucositis (Stomatitis)	29	Patient decision to stop treatment
8	Cost of Medication	19	Nausea and or vomiting	30	Patient entered hospice (date) / /
9	Cough	20	Neutropenia	31	**Disease progression—no response to therapy**
10	Deep Vein Thrombosis	21	Pain	32	Drug was changed
11	Diarrhea	22	Pericardial Effusion	33	Other *please write in*

Table 1: Cancer Protocols and Drugs during Audit Period: PROTOCOL 1

Name of Drug(s) in Protocol 1 (Injection, Infusion, Patch)	Date Prescribed	Dose or Injection (mg per pill or mg/ml)	No. Pills/Day or Injections, Infusions or Patches	Continuous Dosing	Start on Cycle Day	No. of Days On in a Cycle	Number of Days Off in a Cycle	Drug Ongoing	Discontinuation Permanent (P) or Temporary (T) & Date(s)	If stopped (changed), Why? (choose Reason Number below)
Drug 1 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 1	__/__/__			**Yes / No**				**Yes / No**		
Drug 2 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 2	__/__/__			**Yes / No**				**Yes / No**		
Drug 3 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 3	/ /			**Yes / No**				**Yes / No**		

Use this table to determine the **Reason Number** to complete the final column 'If Stopped, changed or discontinued...' above. Write in all that apply

#	Reason	#	Reason	#	Reason - Delay of Drugs / Stoppage
1	Anemia	12	Dyspnea (Shortness of Breath)	23	Peripheral Neuropathy
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3	Arthralgias/Myalgias	14	Fatigue (Asthenia, Lethargy, Malaise)	25	Pulmonary problems
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8	Cost of Medication	19	Nausea and or vomiting	30	Patient entered hospice (date) / /
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Table 1: Cancer Protocols and Drugs during Audit Period: PROTOCOL 1

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Drug 1 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 1	__/__/__			**Yes / No**				**Yes / No**		
Drug 2 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 2	__/__/__			**Yes / No**				**Yes / No**		
Drug 3 (Protocol 1):	__/__/__			**Yes / No** *(Circle one)*				**Yes / No** *(Circle one)*	**P or T (date stopped)** (circle one) __/__/__ Date restart if T __/__/__ If intermittent circle one: Cycle continued; Cycle reset from restart date	
Dose Change Drug 3	/ /			**Yes / No**				**Yes / No**		

Use this table to determine the **Reason Number** to complete the final column 'If Stopped, changed or discontinued...' above. Write in all that apply

#	Reason	#	Reason	#	Reason - Delay of Drugs / Stoppage
1	Anemia	12	Dyspnea (Shortness of Breath)	23	Peripheral Neuropathy
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3	Arthralgias/Myalgias	14	Fatigue (Asthenia, Lethargy, Malaise)	25	Pulmonary problems
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8	Cost of Medication	19	Nausea and or vomiting	30	Patient entered hospice (date) / /
9	Cough	20	Neutropenia	31	**Disease progression—no response to therapy**
10	Deep Vein Thrombosis	21	Pain	32	Drug was changed
11	Diarrhea	22	Pericardial Effusion	33	Other *please write in*

PATIENT COMPLICATIONS, TOXICITY AND SIDE EFFECTS (C/SE) DURING CURRENT ORAL AGENT AUDIT TREATMENT PERIOD

Table 2 is a summary from the NCI toxicity criteria that you may use for all complications and side effects (C/SE). Please date the C/SE. For all C/SE, please check and estimate toxicity if it is not stated explicitly then make grade not known (check box Grade Unknown).

PLEASE CHECK GRADE AT MOST SEVERE LEVEL AND DATE WHEN IT OCCURRED.

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	**Documented in chart? Yes / No**	**Date Noted in Chart**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade Unknown** *Check if not known*
1. Anemia			☐10.0/gdl or higher; 100g/L	☐8.0-10.0/gdl; <100-80 g/L	☐6.5-7.9/gdl; <80-65 g/L	☐<6.5/gdl; <65 g/L	☐
2. Anorexia			☐Loss of appetite without alteration in eating	☐Oral intake altered without weight loss or malnutrition; oral nutrition supplement	☐Weight loss or malnutrition (e.g., inadequate oral caloric or fluid intake); IV fluids or TPN	☐Life-threatening consequences	☐
3. Arthralgias/ Myalgias			☐Mild pain with inflammation	☐Moderate or severe, transient pain with swelling and inflammation	☐Severe, unrelenting pain with joint suffering; interfere with ADL	☐Immobility, unable to move	☐
4. Bleeding/Hemorrhage			☐Mild without transfusion; few symptoms <Male 4.7 – 6.1 million per MCL (write in levels) <Female 4.2 – 5.4 million per MCL (write in levels)	☐Symptomatic loss of 1 liter of blood	☐Transfusion indicated; 2 liters of blood	☐Catastrophic bleeding, major blood replacement	☐
5. Confusion/Hallucination			☐Mild disorientation or mild hallucinations / Perceptual distortions	☐Moderate disorientation limiting ADL / Moderate hallucinations	☐Severe disorientation limiting self care & safety / Severe & frequent hallucinations	☐Life threatening, totally unmanageable, threats of harm to self or others / Threats due to hallucinations, needs hospitalization	☐
6. Constipation			☐Mild	☐Moderate	☐Severe	☐Ileus> 96hrs	☐
7. Cough			☐Dry hacking	☐Dry cough, treatment needed	☐Unrelenting, interferes with sleep and ADL	☐Severe continuous wet cough	☐

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	**Documented in chart? Yes / No**	**Date Noted in Chart**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade Unknown** *Check if not known*
8. Dehydration			☐↑ Oral fluids indicated; dry mucous membrane; ↓ skin turgor	☐IV fluids indicated <24 hours	☐IV fluids indicated ≥24 hours	☐Life-threatening consequences (e.g., hemodynamic collapse)	☐
9. Diarrhea			☐↑ of 2-3 stools /d over pre-Rx	☐↑ of 4-6 stools/d moderate cramping nocturnal stools	☐↑ of 7-9 stools/d severe cramping incontinence	☐↑ of >10 stools/d parenteral support grossly bloody stools	☐
10. Dyspnea (shortness of breath)			☐Dyspnea on exertion, can walk 1 flight of stairs without stopping	☐Dyspnea on exertion unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping	☐Dyspnea with ADL	☐Dyspnea at rest; intubation/ventilator indicated	☐
11. Edema; limb, facial			☐5-10% inter-limb discrepancy in volume or circumference visible difference; swelling; pitting edema	☐>10-30% inter-limb discrepancy in volume or circumference apparent obstruction of anatomic structure; obliteration of skin folds	☐>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	☐Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	☐
12. Fatigue (asthenia, lethargy, malaise)			☐Mild fatigue over baseline	☐Causing difficulty performing ADL	☐Severe fatigue interfering with ADL	☐Disabling	☐
13. Febrile Neutropenia (ANC <1.0x109/L, fever >38.5°C)			☐38.0 – >39.0°C (100.4 – 102.2°F) with neutropenia	☐39.0 – >40.0°C (102.3 – 104.0°F) with neutropenia	☐ ≤40.0°C (≤104.0°F) for ≤24 hours with neutropenia	☐Life-threatening (e.g., septic shock, hypotension, acidosis) ≤40.0°C (≤104.0°F) for >24 hrs with hypotension	☐
14. Fever without Neutropenia			☐38.0 – >39.0°C (100.4 – 102.2°F)	☐39.0 – >40.0°C (102.3 – 104.0°F)	☐ ≤40.0°C (≤104.0°F) for ≤ 24 hours	☐ ≤104°F for 24 hours with shock like symptoms	☐
15. Hand and Foot Skin Reaction			☐Skin changes; no pain	☐Skin changes with pain; no functional interference; peeling, blisters	☐Skin changes interfering with function; pain, ulcers, edema	☐Disability due to function interference and pain	☐

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	**Documented in Chart? Yes / No**	**Date Noted in Chart**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade Unknown** *Check if not known*
16. Hyperglycemia			☐ 160 mg/dL; 8.9 mmol/L	☐ > 160-250 mg/dL; >8.9 – 12.9 mmol/L	☐ > 250-500 mg/dL; 13.9 – 27.8 mmol/L; hospitalization indicated	☐ > 500 mg/dL; >27.8 mmol/L; life-threatening consequences	☐
17. Insomnia (difficulty sleeping)			☐ Occasional, not interfering with function	☐ Interferes with function but not with ADL	☐ Frequent, interfering with ADL	☐ Disabling	☐
18. Memory impairment/ Cognitive Changes			☐ Not interfering with function	☐ Interferes with function, but not interfering with ADL	☐ Interfering with ADL	☐ Amnesia	☐
19. Mucositis / Stomatitis			☐ Erythema, painless ulcers, mild soreness	☐ Painful erythema, edema, ulcers can eat	☐ Painful erythema, edema, ulcers	☐ Parenteral or enteral support	☐
20. Nausea			☐ Able to eat but lack of appetite	☐ About to eat, diminished intake	☐ Unable to eat, 0 intake, inadequate fluids, dehydration, weight loss	☐ Life threatening	☐
21. Pain			☐ Mild, not interfering with function	☐ Moderate, interfering with function, but not interfering with ADL	☐ Severe, interfering with ADL	☐ Disabling	☐
22. Platelets (PLT) (x 1000/mm3)			☐ <75.0x10^9/L <75000/mm^3	☐ ≥50.0-<74.9x10^9/L ≥50000-<75000/mm^3	☐ ≥25.0-<50x10^9/L ≥10000-≤20000/mm^3	☐ <10.0x10^9/L-<25.0x10^9/L <10000/mm^3	☐
23. Pruritus			☐ Mild or localized	☐ Intense, widespread, little to no discomfort	☐ Widespread with discomfort	☐ Widespread, open and weeping discomfort	☐
24. Skin/Macular/Rash			☐ Scattered macular or popular rash or erythema that is asymptomatic	☐ Scattered macular or papular rash or erythema with pruritus or other symptoms	☐ Generalized symptomatic macular, popular, or vesicular rash	☐ Exfoliative or ulcerating dermatitis	☐
25. Vomiting			☐ 1 episode in 24 hours	☐ 2-5 episodes in 24 hours; IV fluids indicated <24 hours	☐ ≥6 episodes in 24 hours; IV fluids, or TPN indicated ≥24 hours	☐ Life-threatening consequences	☐

Table 2: Patient Complications, Symptoms, Toxicity and Side Effects (C/SE) During Current Oral Agent Treatment Period

PLEASE CHECK THE APPROPRIATE GRADE							
Adverse Effect/Complication	Documented in Chart? Yes / No	Date Noted in Chart	Grade 1	Grade 2	Grade 3	Grade 4	Grade Unknown *Check if not known*
26. WBC (Neutropenia - x100/mm3)			☐<3.0-3.9x10^9/L <3000/mm^3	☐<2.0-2.9x10^9/L ≥2000-2900/mm^3	☐<1.0-1.9x10^9/L ≥1000-<1900/mm^3	☐<1.0x10^9/L <1000/mm^3	☐
27. Other e.g. wound infections, neurological events, pathological fractures *(write in & describe)*							☐

DOCUMENTATION IN THE MEDICAL ELECTRONIC RECORD

Evidence of oral cancer medication not being available, or availability	□ Yes	□ No
Is there a record that patient received discussion about financial assistance for oral cancer medication (insurance or social worker)?	□ Yes	□ No
Is there evidence of any discussion of medication cost concerns with patient?	□ Yes	□ No
Is there any documentation of patient training or education about oral cancer medication?	□ Yes	□ No
If yes, was it a: Pharmacy	□ Yes	□ No
Patient education (classes or instruction)	□ Yes	□ No
Specialty pharmacy	□ Yes	□ No
Is there any documentation of adherence / non adherence with oral cancer medication?	□ Yes	□ No
Is there any documentation of follow up calls to check on patient's oral cancer medication, or any side effects from medication?	□ Yes	□ No

Complete Table 3

PRESCRIBED MEDICATIONS OTHER THAN CHEMO OR ORAL CANCER MEDICATIONS LISTED IN TABLE 1

Please list all medications (other than chemotherapy agents listed in Table 1) that were prescribed during the audit period, as well as medications that the patient was on for comorbid conditions during the audit period.

Table 3: Prescribed Medications

NAME OF DRUG	DATE PRESCRIBED

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX E: Parent Study Screening/Baseline Data Collection Tools

What is your highest level of education completed?
o No formal education
o Completed grade school
o Completed some high school
o Completed high school
o Completed some college or technical college or associate degree
o Completed college
o Completed graduate/professional degree (post baccalaureate degree)
o Refused

What is your current marital status?
o Never married
o Married
o Divorced/Separated o Widowed
o Living together
o Refused

What is your ethnic background?
o Hispanic or Latino
o Not Hispanic or Latino
o Unknown
o Refused

What is your race or ethnic background?
o American Indian or Alaskan Native
o African American or Black
o Asian
o Native Hawaiian or Pacific Islander o White
o More than one race
o Unknown
o Refused

Gender:
o Male
o Female

Ethnicity:
o Hispanic/Latino
o Not Hispanic/Latino

Screening Eligibility Form from Parent Study
(Collecting patient and disease characteristics)

Race (check all that apply):
o American Indian/Alaska Native
o Asian
o Native Hawaiian/Pacific Islander
o Black/African American
o White

Cancer Site:
o Breast
o Colorectal
o Gastrointestinal
o Leukemia
o Liver
o Lung
o Lymphoma
o Melanoma
o Myeloma
o Pancreatic
o Prostate
o Renal
o Sarcoma

Stage:
o I
o II
o III
o IV
o Other
If 'Other' write in stage: _____

On Concurrent IV chemotherapy?:
o Yes
o No
o If yes, medication and frequency:_____ o

On Concurrent Radiation?
o Yes
o No
o If yes, treatment name and frequency: _____

Patient Eligibility:
o Yes o No
(If NO to ANY of the questions below, patient is NOT eligible)

Can hear on telephone?
o Yes o No

Can read and understand English?

o Yes o No

21 or older?
o Yes
o No
o Age:_____

ECOG Performance status within 0-2 or Karnofsky performance status within 50-100?
o Yes
o No
o Score:_____

Has a land line/cell phone with touch pad numbers?
o Yes o No

Is on an eligible oral cancer medications?
o Yes o No

Eligibility:
o Eligible o Ineligible

Enrollment Status:
o Consented
o Refused
o Lost to follow-up

Reason, if refused:
o Too ill
o Too busy
o Lack of interest
o Other

Date Screened: _____ Recruiter Initials: _____

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

APPENDIX F: Cancer Symptom Experience Inventory

1. In the past 7 days have you experienced **fatigue** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your fatigue at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did fatigue interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
2. In the past 7 days have you experienced **sleep disturbance** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your sleep disturbance at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did sleep disturbance interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
3. In the past 7 days have you experienced **anxiety** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your anxiety at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did anxiety interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
4. In the past 7 days have you experienced **weakness** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		

a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your weakness at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did weakness interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
5. In the past 7 days have you experienced **pain** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your pain at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did pain interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
6. In the past 7 days have you experienced **headaches** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your headaches at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did headaches interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
7. In the past 7 days have you experienced **skin rash or skin sores** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your skin rash or skin sores at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did skin rash or skin sores **fatigue** interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10

Did not interfere ---------- Interfered completely										Refused
8. In the past 7 days have you experienced **numbness or tingling, especially in hands or feet** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your numbness or tingling, especially in hands or feet at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did numbness or tingling, especially in hands or feet interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
9. In the past 7 days have you experienced **redness, peeling or pain in hands or feet** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your redness, peeling or pain in hands or feet at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did redness, peeling or pain in hands or feet interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
10. In the past 7 days have you experienced **swelling of hands or feet** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your swelling of hands or feet at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did swelling of hands or feet interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
11. In the past 7 days have you experienced **joint pain** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		

a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your joint pain at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did joint pain interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
12. In the past 7 days have you experienced **sores in mouth** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your sores in mouth at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did sores in mouth interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
13. In the past 7 days have you experienced **lack of appetite** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your lack of appetite at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did lack of appetite interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
14. In the past 7 days have you experienced **nausea or vomiting** related to your cancer or its treatment? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your nausea or vomiting at its WORST in the past 7 days. *(Circle one response)*										
1	2	3	4	5	6	7	8	9	10	
Very little ---------- Worst possible									Refused	
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did nausea or vomiting interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10

Did not interfere ---------- Interfered completely										Refused

15. In the past 7 days have you experienced **diarrhea** related to your cancer or its treatment? *(Circle one response)*

1	2	3
Yes	No	Refused

a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your diarrhea at its WORST in the past 7 days. *(Circle one response)*

1	2	3	4	5	6	7	8	9	10
Very little ---------- Worst possible									Refused

b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did diarrhea interfere in your daily activities in the last 7 days? *(Circle one response)*

0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused

16. In the past 7 days have you experienced **constipation** related to your cancer or its treatment? *(Circle one response)*

1	2	3
Yes	No	Refused

a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your constipation at its WORST in the past 7 days. *(Circle one response)*

1	2	3	4	5	6	7	8	9	10
Very little ---------- Worst possible									Refused

b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did constipation interfere in your daily activities in the last 7 days? *(Circle one response)*

0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused

17. In the past 7 days have you experienced **cough** related to your cancer or its treatment? *(Circle one response)*

1	2	3
Yes	No	Refused

a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your cough at its WORST in the past 7 days. *(Circle one response)*

1	2	3	4	5	6	7	8	9	10
Very little ---------- Worst possible									Refused

b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did cough interfere in your daily activities in the last 7 days? *(Circle one response)*

0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused

18. In the past 7 days have you experienced **shortness of breath** related to your cancer or its treatment? *(Circle one response)*

1	2	3
Yes	No	Refused

a. **If Yes:** Please rate on a scale from 1-9, with 1 being very little, to 9 being worst possible, your shortness of breath at its WORST in the past 7 days. *(Circle one response)*

1	2	3	4	5	6	7	8	9	10
Very little ---------- Worst possible									Refused
b. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did shortness of breath interfere in your daily activities in the last 7 days? *(Circle one response)*									
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
19. In the past 7 days did you or anyone else including your doctor take your temperature? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
a. **If Yes:** Was your temperature above 101 degrees Fahrenheit? *(Circle one response)*										
1				2				3		
Yes				No				Refused		
i. **If Yes:** On a scale of 0 – did not interfere, to 9 – interfered completely, overall how much did your fever interfere in your daily activities in the last 7 days? *(Circle one response)*										
0	1	2	3	4	5	6	7	8	9	10
Did not interfere ---------- Interfered completely										Refused
ii. **If Yes:** Did you report your fever to your oncologist? *(Circle one response)*										
1				2				3		
Yes				No				Refused		

Given, B.A., Given, C.W., & Sikorskii (2013–2017). Improving adherence to oral cancer agents and self care of symptoms using an IVR (1R01CA162401-O1A1). [National Cancer Institute clinical trial]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02043184.

REFERENCES

REFERENCES

1. Pefoyo AJ, Bronskill SE, Gruneir A, et al. The increasing burden and complexity of multimorbidity. *BMC Public Health.* 2015;15(415).

2. Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. *Journal of Geriatric Oncology.* 2016;7(4):249-257.

3. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC Med.* 2012;10(68).

4. Eton DT, Elraiyah TA, Yost KJ, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. *Patient Related Outcome Measures.* 2013;4:7-20.

5. Sav A, King MA, Whitty JA, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. *Health Expectations: An International Journal of Public Participation in Health Care and Health Policy.* 2013;18(3):312-324.

6. Tran VT, Barnes C, Montori VM, Falissard B, Ravaud P. Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions. *BMC Med.* 2015;13(115).

7. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med.* 2014;12(109).

8. Eton DT, Ridgeway JL, Egginton JS, et al. Finalizing a measurement framework for the burden of treatment in complex patients with chronic conditions. *Patient Related Outcome Measures.* 2015;6:117-126.

9. Gao X, Nau DP, Rosenbluth SA, Scott V, Woodward C. The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS care.* 2000;12(4):387-398.

10. Lepine JP, Briley M. The increasing burden of depression. *Neuropsychiatric Disease and Treatment.* 2011;7(Suppl 1):3-7.

11. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatric Services (Washington, DC).* 2014;65(8):977-987.

12. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care.* 2004;27(7):1535-1540.

13. Stange D, Kriston L, von-Wolff A, Baehr M, Dartsch DC. Reducing cardiovascular medication complexity in a German university hospital: effects of a structured pharmaceutical management intervention on adherence. *Journal of Managed Care Pharmacy : JMCP.* 2013;19(5):396-407.

14. Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *Journal of Cystic Fibrosis : Official Journal of the European Cystic Fibrosis Society.* 2013;12(5):461-467.

15. Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. *The American Journal of Gastroenterology.* 2014;109(9):1304-1311.

16. Ridgeway JL, Egginton JS, Tiedje K, et al. Factors that lessen the burden of treatment in complex patients with chronic conditions: a qualitative study. *Patient Preference and Adherence.* 2014;8:339-351.

17. Lhuilier D, Brugeilles F, Rolland D. [Chronic disease and treatment burden for patients: the example of hepatitis C]. *Sante publique (Vandoeuvre-les-Nancy, France).* 2015;27(1 Suppl):S17-21.

18. Presley CJ, Soulos PR, Tinetti M, Montori VM, Yu JB, Gross CP. Treatment Burden of Medicare Beneficiaries With Stage I Non-Small-Cell Lung Cancer. *Journal of oncology Practice / American Society of Clinical Oncology.* 2016;13(2):398-e107.

19. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer.* 2008;16(7):791-801.

20. Cheng AC, Levy MA. Data Driven Approach to Burden of Treatment Measurement: A Study of Patients with Breast Cancer. *AMIA Annual Symposium proceedings AMIA Symposium.* 2016;2016:1756-1763.

21. Winn AN, Keating NL, Dusetzina SB. Factors Associated With Tyrosine Kinase Inhibitor Initiation and Adherence Among Medicare Beneficiaries With Chronic Myeloid Leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(36):4323-4328.

22. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin.* 2016;66(4):337-350.

23. Sun V, Grant M, Wendel CS, et al. Sexual Function and Health-Related Quality of Life in Long-Term Rectal Cancer Survivors. *The Journal of Sexual Medicine.* 2016;13(7):1071-1079.

24. Verbrugghe M, Duprez V, Beeckman D, et al. Factors Influencing Adherence in Cancer Patients Taking Oral Tyrosine Kinase Inhibitors: A Qualitative Study. *Cancer Nursing.* 2016;39(2):153-162.

25. Spoelstra SL, Given CW, Sikorskii A, Majumder A, Schueller M, Given BA. Treatment With Oral Anticancer Agents: Symptom Severity and Attribution, and Interference With Comorbidity Management. *Oncology Nursing Forum.* 2015;42(1):80-88.

26. Bassan F, Peter F, Houbre B, et al. Adherence to oral antineoplastic agents by cancer patients: definition and literature review. *European journal of Cancer Care.* 2014;23(1):22-35.

27. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. *Cancer Treat Rev.* 2014;40(1):102-108.

28. Arthurs G, Simpson J, Brown A, Kyaw O, Shyrier S, Concert CM. The effectiveness of therapeutic patient education on adherence to oral anti-cancer medicines in adult cancer patients in ambulatory care settings: a systematic review. *JBI Database of Systematic Reviews and Implementation Reports.* 2015;13(5):244-292.

29. Hall AE, Paul C, Bryant J, et al. To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Critical Reviews in Oncology/Hematology.* 2016;97:247-262.

30. Zerillo JA, Goldenberg BA, Kotecha RR, Tewari AK, Jacobson JO, Krzyzanowska MK. Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review. *JAMA Oncology.* 2018;4(1):105-117.

31. Accordino MK, Hershman DL. Disparities and challenges in adherence to oral antineoplastic agents. *American Society of Clinical Oncology Educational Book / ASCO American Society of Clinical Oncology Meeting.* 2013:271-276.

32. Trivedi D, Landsman-Blumberg P, Darkow T, Smith D, McMorrow D, Mullins CD. Adherence and persistence among chronic myeloid leukemia patients during second-line tyrosine kinase inhibitor treatment. *Journal of Managed Care & Specialty Pharmacy.* 2014;20(10):1006-1015.

33. McNamara E, Redoutey L, Mackler E, Severson JA, Petersen L, Mahmood T. Improving Oral Oncolytic Patient Self-Management. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2016;12(9):e864-869.

34. Salgado TM, Mackler E, Severson JA, et al. The relationship between patient activation, confidence to self-manage side effects, and adherence to oral oncolytics: a pilot study with Michigan oncology practices. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer.* 2017;25(6):1797-1807.

35. Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. *Cancer Treat Rev.* 2013;39(6):610-621.

36. Dusetzina SB, Huskamp HA, Winn AN, Basch E, Keating NL. Out-of-Pocket and Health Care Spending Changes for Patients Using Orally Administered Anticancer Therapy After Adoption of State Parity Laws. *JAMA Oncology.* 2017;4(6): e173598.

37. Niccolai JL, Roman DL, Julius JM, Nadour RW. Potential Obstacles in the Acquisition of Oral Anticancer Medications. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2017;13(1):e29-e36.

38. Kaisaeng N, Harpe SE, Carroll NV. Out-of-pocket costs and oral cancer medication discontinuation in the elderly. *Journal of Managed Care & Specialty Pharmacy.* 2014;20(7):669-675.

39. Kimura M, Nakashima K, Usami E, et al. Adherence and awareness of the therapeutic intent of oral anticancer agents in an outpatient setting. *Oncology Letters.* 2015;9(5):2341-2346.

40. Kimura M, Usami E, Iwai M, et al. Oral anticancer agent medication adherence by outpatients. *Oncology Letters.* 2014;8(5):2318-2324.

41. Sikorskii A, Given CW, Given BA, et al. Do treatment patterns alter beliefs cancer patients hold regarding oral oncolytic agents? *Psycho-Oncology.* 2018;27(3):1005-1012.

42. Karnofsky DA. The clinical evaluation of chemotherapeutic agents in cancer. *Evaluation of Chemotherapeutic Agents.* 1949:191-205.

43. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology.* 1982;5(6):649-655.

44. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. *The Annals of Pharmacotherapy.* 2004;38(9):1369-1376.

45. Given B, Given CW, Sikorskii A, et al. Establishing mild, moderate, and severe scores for cancer-related symptoms: how consistent and clinically meaningful are interference-based severity cut-points? *Journal of Pain and Symptom Management.* 2008;35(2):126-135.

46. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology.* 1986;51(6):1173-1182.

47. Spoelstra SL, Given CW, Sikorskii A, Majumder A, Schueller M, Given BA. Treatment With Oral Anticancer Agents: Symptom Severity and Attribution, and Interference With Comorbidity Management. *Oncology Nursing Forum.* 2015;42(1):80-88.

48. Kawakami K, Nakamoto E, Yokokawa T, et al. Patients' self-reported adherence to capecitabine on XELOX treatment in metastatic colorectal cancer: findings from a retrospective cohort analysis. *Patient Preference and Adherence.* 2015;9:561-567.

49. Lo PC, Dahlberg SE, Nishino M, et al. Delay of treatment change following objective progression on first-line erlotinib in EGFR-mutant lung cancer. *Cancer.* 2015;121(15):2570-2577.

50. Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: the role of the midlevel practitioner. *The Journal of Supportive Oncology.* 2012;10(1):14-24.

51. Dasanu CA. Length of adjuvant imatinib therapy in GIST: weighing benefits, side effects and costs. *Journal of Oncology Pharmacy Practice: Official Publication of the International Society of Oncology Pharmacy Practitioners.* 2012;18(3):379-380.

52. van Leersum NJ, Janssen-Heijnen ML, Wouters MW, et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. *International Journal of Cancer.* 2013;132(9):2157-2163.

53. Tawfik B, Pardee TS, Isom S, et al. Comorbidity, age, and mortality among adults treated intensively for acute myeloid leukemia (AML). *Journal of geriatric oncology.* 2016;7(1):24-31.

54. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. *Clinical Epidemiology.* 2013;5(Suppl 1):3-29.

CHAPTER FIVE: CONCLUSIONS

Introduction

The purpose of this dissertation was to examine the concept of burden of treatment (BOT) within cancer patients with multimorbid conditions. This examination was done both conceptually and operationally. Three manuscripts were developed in order to address the gaps in the current BOT and cancer literature. The first manuscript was a concept analysis that examined burden of treatment specifically within cancer patients with multimorbid conditions. A conceptual model was developed to examine the relationship between the antecedents, attributes, and consequences of the concept of BOT within cancer patients with multimorbid conditions.

The final two manuscripts were secondary analyses of a randomized controlled trial (RCT) that tested an adherence and symptom management intervention within cancer patients that were newly prescribed oral oncolytic agents (OOA).[1] Participants in the parent trial were recruited from six National Cancer Institute (NCI) designated comprehensive cancer centers. After consenting, participants completed baseline telephone interviews, which gathered information regarding their OOA regimens; medication beliefs; adherence; medication coverage; multimorbid conditions; symptoms; mental and physical functioning; depression; interaction with healthcare providers; demographics; and health insurance.

After completing the baseline interview, participants were randomized to either the experimental or control (normal care) group. The experimental group received an adherence intervention, which involved an interactive voice response (IVR) system notifying participants each time they had to take a dose of their OOAs. Additionally, the experimental group was given a symptom management toolkit (SMT). Participants were referred to the SMT when rating the severity of a symptom ≥4/10 on the Cancer Symptom Experience Inventory (CSEI) severity scale.[2] The SMT provided strategies for patients to manage the particular symptom. Telephone

interviews with each participant occurred at four intervals for 12 weeks. After which, medical record audits (MRA) were completed by trained auditors at each of the recruitment sites. Auditors collected clinical information, including cancer diagnosis history; interaction with healthcare providers; cancer treatment regimen prescriptions; toxicities; and non-cancer treatment medications.

The final two manuscripts of this dissertation utilized portions of the data from the parent trial study. The purpose of manuscript two was to examine the amount of time between when a participant's initial OOA prescription was written, and when they actually received and started taking the OOA medication. The analysis also examined whether certain cancer treatment and healthcare system factors may impact the amount of time it took for patients in the parent trial to receive their OOAs. Finally, manuscript three examined the relationship between baseline antecedent factors (patient, social, disease/treatment, and healthcare system) and temporary stoppages of patients' OOA regimens. Additionally, the analysis explored how BOT-indicator variables might moderate this relationship.

The overall purpose of this dissertation was to add to the limited current body of literature regarding BOT, specifically within cancer patients with multimorbid conditions, from a conceptual and operational standpoint. Conceptually, this work aimed examine BOT within cancer patients with multimorbid conditions, which has not been done within this population. Operationally, this dissertation provided new knowledge regarding the challenges that cancer patients prescribed OOAs experience in acquiring their medications. Additionally, this work examined how multimorbid conditions and increased BOT impacts patients' continuation of their OOA regimens, specifically temporary stoppages of their treatment. This work was completed with the hope to add new knowledge and insight into the developing BOT literature, as well as to lay a foundation for a program of research focused on decreasing the BOT for cancer patients with multimorbid conditions.

Overview of Manuscript One

Manuscript one expanded on the burden of treatment conceptual literature that has been done by Tran et al.,[3-5] Eton et al.,[6,7] and Sav et al.[8] Unlike these previous works, this manuscript focused specifically on the population of cancer patients with multimorbid conditions. The conceptual analysis was guided by Rodgers' concept analysis method, which works well for dynamic concepts that continue to change over time.[9] The components of BOT can continuously change, and therefore, Rodgers' model was a proper framework to follow. A systematic search was carried out across a number of databases and disciplines. In order to capture as many eligible articles as possible, certain multimorbid conditions commonly associated with cancer were included in as keywords in the search terms, such as diabetes and cardiovascular disease. After removing duplicates and articles with no abstracts, all titles and abstracts (n = 1938) were screened for eligibility. This abstract screening resulting in 84 full text articles, which were then reviewed, in their entirety, for inclusion within the concept analysis. After selecting the 29 articles for inclusion, antecedents, attributes and consequences were identified from these articles.

The attributes of BOT are divided into two primary components: patient workload and patient perspective. Much like the previous BOT works, a major attribute of BOT was patient workload. Patient workload is the tasks required of an individual to manage their condition(s). Patient workload was further divided into the following subcategories: disease and treatment demands, interaction with the healthcare system, and financial responsibilities. These three subcategories involve tasks that are required of patients in order to manage their cancer and multimorbid conditions. This manuscript found that overall, as the number of multimorbid conditions increased, the workload for all three subcategories increased, as well.[10-28] The attribute of BOT, patient perspective, is concerned with the subjective viewpoint of one's conditions and associated workload. While the majority of the included studies discussed workload, only a few studies focused on the patient perspective.[13,20,26] These three studies

examined how multimorbid conditions and healthcare tasks impact individuals' daily lives, their ability to cope with their disease and workload, and individuals' perception of their relationship with providers.

Before BOT can occur, there are some, or all, antecedent factors that must take place. This concept analysis identified four antecedent categories related to BOT, which include patient factors, social factors, disease/treatment factors, and healthcare system factors. Certain factors can contribute to an increased burden of treatment, such as older age, lack of a support system, advanced cancer, multimorbid conditions, and poor access to care.[10,12,14,17,18,20,21,23-26,29-32] While these antecedents can impact attributes of BOT, they can also have a direct impact on certain consequences, or outcomes. The consequences most commonly examined in the included articles were broken down into four categories: adherence/non-adherence, clinical outcomes, treatment modifications, and health and well-being. In general, individuals with cancer and multimorbid experienced worse consequences than those with cancer alone.

The purpose of manuscript one was to increase the knowledge within the burden of treatment literature, as well as the cancer and multimorbidity literature. In general, the included articles concluded that multimorbidity among cancer patients resulted in an increased BOT and led to poor consequences, including adherence, clinical outcomes, treatment modifications, and health and well-being. The previous BOT works have focused extensively on patient workload, but minimally on the patient perspective. Although there were a limited number of included articles, this work described how cancer patients with multimorbid conditions perceive the impact of their conditions and workload on their daily lives. BOT is a complex concept that will continue to be vital as the life expectancy remains high and the number of individuals with cancer and multimorbid conditions continues to rise. This work developed a conceptual model, in order to provide insight for researchers and clinicians to care for a growing, vulnerable population.

Overview of Manuscript Two

Manuscript two focused on amount of time patients in the parent trial had to wait to receive their OOAs. OOA prescriptions are not as easily filled as other medications. In most cases, only certain specialty and mail-order pharmacies are able to fulfill OOA prescriptions.[33,34] Therefore, patients are not able to easily access medications as they are for common medications, such as beta blockers for hypertension. For this reason, this work aimed to examine the time to OOA receipt and what barriers might increase this amount of time. This secondary data analysis examined the number of days from when patient's initial OOA prescription was written by their oncologist until the patient received the drug in hand. In addition to describing this number of days to receipt, this work examined how OOA drug class, type of insurance, recruitment site, and whether or not the patient had an out-of-pocket copay for the OOA might impact the number of days to receipt.

The results of this secondary analysis showed that patients in this parent trial waited on average 10 days (SD = 14.5) to receive their first OOA prescription. Although the mean number of days was 10, the range of time for patients to receive their initial prescription was from 0-135 days. Unadjusted means showed little difference in days to receipt between those with private/commercial and government insurance, while individuals without an OOA copay waited almost one day longer than those that did have a copay. Patients from one recruitment site waited nearly 3.5 days more than the recruitment site with the second longest wait time. Patients prescribed OOAs in the "other" OOA drug class waited longer than those prescribed any of the other three OOA drug classes. The analysis of variance (ANOVA) showed that insurance type made a significant difference on days to receipt, with those that did have a copay actually waiting longer, after taking into account the other variables in the model. There was also a significant three-way interaction between copay, insurance type, and drug class. After running simple interaction effects, the results showed that type of insurance may have a difference on the number of days to receipt, depending on whether or not an individual had a

copay and what drug class they were prescribed. Thus, the amount of time a patient has to wait receive their OOA prescription may vary depending on an individual's insurance plan, whether or not they have an out-of-pocket cost, and the specific OOA they are prescribed.

The majority of patients prescribed OOAs have advanced cancer and have failed multiple lines of treatment, and therefore, are in a critical point in their care trajectory. This work aimed to determine how many days patients have to wait until receiving their first OOA prescription. This work only examined the initial prescription, but not subsequent refills. Patients in the parent trial experienced delays in receiving subsequent refill as well, which can cause distress and burden for patients during this critical period of care. This work demonstrates the need for continued research into the process of patients filling OOA prescriptions, and what can be done in practice to decrease the number of days for initial prescription and subsequent refill times. Future work should examine each step of the OOA process, in order to determine what factors might contribute the greatest number of days to patients' acquisition time. Additionally, future work should continue to assess patient wait times for subsequent refills and what events might be delaying patient acquisition, such as prescription error or pharmacy shipment delays.

Overview of Manuscript Three

Manuscript three was a secondary analysis of the parent trial that applied the conceptual model developed in manuscript one. The purpose of manuscript three was to examine the moderation effect of burden of treatment on the relationship between baseline antecedent characteristics and temporary stoppages of patients' OOA regimens. The baseline antecedent factors included variables from all four of the antecedent domains. These variables included: patient – age, sex, and employment status; social – marital status; disease/treatment – multimorbid conditions and OOA drug class; and healthcare system: type of insurance and OOP cost. The burden of treatment indicator variables used were an OOA regimen complexity score[35] for patient workload and patient symptom interference on daily activities[2] for the patient perspective. The

outcome variable was whether or not an individual experienced a temporary stoppage of their OOA regimen during the parent trial.[1]

The results showed that more than 36% (n = 99) of the patients in the parent trial experience a temporary stoppage of their cancer treatment regimen. Forty percent of patients with 4+ multimorbid conditions experienced a temporary stoppage (n = 40), while only 19% of individuals with no multimorbid conditions experienced a temporary stoppage (n = 4). The moderation models showed that the BOT moderation, interaction terms were non-significant. Females ($P = .018$) and patients prescribed kinase inhibitors ($P < .01$) were significantly more likely to experience a temporary stoppage during the parent trial.

In monitoring patients for such a short time, 12 weeks, this secondary analysis showed how frequent modifications can occur for patients prescribed OOAs. With the majority of cancer patients prescribed OOAs having advanced disease, it is critical for these patients to be receiving an effective dose as continuously as possible. However, rest periods are necessary for some patients, as this work shows. Although non-significant in the moderation models, this work showed a trend of individuals with more multimorbid conditions experiencing a greater percentage of temporary stoppages than those with no multimorbid conditions. It was hypothesized that BOT would have some impact on the relationship between baseline characteristics and treatment modifications. However, this did not hold true, possibly due to the utilization of BOT-indicator variables rather than BOT-specific measures. Future research should further examine the impact of multimorbid conditions and medications impact on cancer patients' continuation of treatment. Additionally, the development and utilization of BOT-specific measures are needed to examine BOT within this population.

Limitations

Although this work provides new knowledge and insight to a limited body of literature, it is not without its limitations. There are limitations in utilizing a secondary analysis, as well as some components of the parent trial. The parent trial recruited patients from the Midwest United

States, and therefore, may not be generalizable to the rest of the country. The sample was not very racially diverse, with 89% of the sample being Caucasian. The mean age of the sample was over 61 years old and only included 8 patients under the age of 35, indicating a need for future research to include younger patients. With the majority of recruitment sites being academic medical centers, the sample was quite educated. Seventy-three percent of the sample completed at least some college work, which is beyond norm for the US. Hematologic malignancies were underrepresented in the study, only comprising about 10% of the sample. Additionally, the majority of the sample had advanced stage cancer. Because of this sample distribution, the parent trial and this secondary analysis may not be generalized to more racial diverse, younger, early stage cancers, and hematologic populations.

Specifically looking at the secondary analysis, there are limitations based on this study design. The aims of the parent trial were not designed with the research questions of this secondary analysis in mind. Therefore, certain indicator variables were needed, which limits the evidence for burden of treatment. Several variables, including temporary stoppages, were gathered from the parent trial's MRAs. The MRAs were limited electronic health data within the hospital system of each recruitment center. Therefore, if a patient presented to a clinic or hospital outside of the recruitment site hospital system, that data was not attainable. Additionally, multimorbid conditions were based on non-cancer prescription medications collected from the MRA. Reviewing patients' ICD-10 multimorbid condition diagnoses may have yielded more accurate data. This work provides evidence for research utilizing the concept of burden of treatment within cancer patients with multimorbid conditions. However, this future work will need study designs and data collection unique to burden of treatment.

Implications

Nursing Research

This work presents one of the first examinations of burden of treatment within cancer patients with multimorbid conditions, both from a conceptual and operational standpoint. Conceptually,

burden of treatment has been examined within chronic diseases,[8] but no such conceptual analysis could be found specifically within cancer patients with multimorbid conditions. This conceptual work examined the importance of both the patient workload and the subjective patient perspective within burden of treatment. Although the antecedents and consequences were similar to previous conceptual analyses, this work pointed outs examples of the impact of BOT that are unique to cancer patients with multimorbid conditions, such as the impact of BOT on the continuation of cancer treatment.

There a few current studies that have examined burden of treatment within cancer patients,[25,36,37] with one of these articles examining the influence of multimorbid conditions with burden of treatment.[25] This dissertation is unique in that it is the only work that has specifically focused on burden of treatment within cancer patients treated with OOAs, as well as managing multimorbid conditions. Manuscript two examined the challenges faced by patients in acquiring their OOAs, which has the potential to impact their perspective of their disease and workload, while manuscript three examined how BOT and multimorbidity impacts patients' continuation of their cancer treatment, specifically temporary stoppages of OOAs. Research within this population is behind the pace needed to make a substantial impact, given the increase in prevalence of multimorbid condition and the increase of OOAs entering the chemotherapy pipeline each year.[38,39] This work has started to address some of the gaps within this scarce body of literature.

Two of the primary gaps within the BOT literature are the inclusion and examination of patient perspective and the operation of BOT as a whole. As has been briefly discussed, most of the work already done focuses on variables that can easily be quantified that contribute to the workload of being a patient with a chronic disease. Manuscript one showed that individuals with more multimorbid conditions are bothered by their symptoms more than those with cancer alone. Manuscript one also found that lack of family support, stress related to being a minority (i.e. racial, sexual, or socioeconomic status), lack of spiritual support, and being a burden to

caregivers contributed to an increased BOT.[13,20,26] The most common concern for patients was poor communication with providers. Poor communication will providers was associated with increased distress and worse outcomes for individuals with cancer and multimorbid conditions.[13,20] The contributions from manuscript two on patient perspective show that patient workload is not the only contributor to BOT, and that patient perspective can have negative impact on one's ability to manage their conditions and health. However, as has been discussed throughout this dissertation, patient workload comprises the majority of the BOT literature. Future work should focused on incorporating the patient perspective, in order to fully examine the challenges experienced by cancer patients with multimorbid conditions.

The other gap is how to operationalize burden of treatment, both the patient workload and the patient perception of that workload. Patient workload has been operationalized in many different ways, including number of medications, interactions with the healthcare system, and cost. Manuscript three of this dissertation operationalized workload as the complexity of patients' OOA regimens. While, patient perspective was operationalized by patients' ratings of their symptom interference on daily activities. Due using data from a parent trial, BOT-specific measures could not be utilized, nor could other BOT-indicator variables. The BOT-indicator variables that were used in manuscript three were non-significant in the regression models. Utilizing other BOT-indicator variables or BOT-specific measures may have yielded different results. This work points out the need for continued development of BOT-specific measures that will may be able to better examine how cancer patients with multimorbid conditions experience BOT.

Looking specifically at operational outcomes of this dissertation, this work focused on patients' time to acquisition of OOAs and temporary stoppages of OOA regimens. Manuscript two showed that certain disease/treatment and healthcare system variables may impact the time it takes for patients to receive their OOAs. This work only examined the initial OOA prescription, but cited examples within the discussion of patients in the trial study having issues receiving

subsequent OOA refills. Future work in this area should examine each step of the OOA acquisition process, as well as difficulties in patients receiving subsequent refills. Patients prescribed OOAs are in a vulnerable state of their cancer treatment, and being without their drugs can have negative impact on their disease status. Similarly, longer and more frequent stoppages can negatively impact patients' disease status. There was a trend of those with multimorbid conditions experiencing a greater proportion of temporary stoppages. Individuals prescribed certain drug classes were also more likely to experience temporary stoppages.

Regarding manuscript two, a future study could include an intervention that includes an oncology nurse liaison to follow cancer patients from the time when their initial OOA prescription through a number of subsequent refills. The liaison would assist in the initial transition to an OOA regimen by communicating with their insurance company to help speed up the coverage process, as well as be the advocate for patients when communicating with a specialty or mail-order pharmacy. The liaison would also work with patients to ensure refills are being processed on time and patients are receiving subsequent refills in a timely manner. Different than manuscript two, this future study would examine the number of days for each process of the OOA acquisition process. The study would also gather data on what type of pharmacy the patient is using to fill their OOA prescription, specific OOA drug, insurance information, oncology facility they are being treated at, and the financial variables, such as out-of-pocket cost and financial assistance needs. This study would provide a more in-depth understanding of the challenges cancer patients face in acquiring their OOAs.

Regarding manuscript three, future work should further examine the workload of cancer patients with multimorbid conditions, as well as their perspective of their conditions and associated workload. Based on this dissertation, measurement development can begin by including the patient workload identified and ask patients to identify the healthcare tasks they must complete and how often in order to manage their cancer and other conditions. Additionally, the measure would include a subjective component to measure patients perception of their

disease and associated workload. This future work would both help to develop a BOT-specific measure, as well as to inform future studies that would help to decrease BOT experienced by these patients identified by the measure. For example, if patients are having difficulties managing their medications between their cancer treatment and other conditions, an intervention study utilizing in-home visits from a nurse to provides strategies to effectively manage complex medications regimens could be developed. This dissertation found that cancer patients with multimorbid conditions are at risk for a greater BOT than those with cancer alone. Future research should target the specific needs of this population and help to empower patients to effectively manage their cancer and other conditions.

Nursing Practice

As the population continues to age and multimorbidity become more prevalent, developing education and self-management strategies for cancer and multimorbid conditions will be a vital goal for clinicians, especially nurses. With multimorbidity, nurses and other clinicians will be tasked with educating individuals about the interactions of their multimorbid conditions and the associated medications. When individuals are actually treating cancer and other multimorbid conditions, the BOT becomes greater for both the patient and the clinicians. Patients will need to have a better and more comprehensive understanding of their current situations and the status of their multiple conditions.[40-45] Nurses, especially oncology nurses, are in a critical position when it comes to educating patients and caregivers about the necessity for effective self-management. Better patient education and increased communication between clinicians and patients and their caregivers will be vital in working with this population, in order to empower patients to effectively manage their cancer and other conditions.

These three manuscripts have shown evidence for the use of the concept of burden of treatment within the growing population of cancer patients with multimorbid conditions. This work shows which groups of people may be at risk for a greater burden of treatment and subsequently poor outcomes. Clinicians can focus on these patients to provide more education

and resources to ensure that they are better equipped to manage their OOAs and multimorbid conditions. Cancer patients actively receiving treatment and managing other conditions are in a vulnerable state. Currently, there are no standards of care for patients actively being treated with OOAs and taking medications for multimorbid conditions. Standards for screening patients for appropriateness of OOA treatment regimens should be put into place, while taking into account patients' other conditions and the medications they are prescribed. Nurses are in a critical position to help ease the burden of treatment through being an advocate for patients to ensure they receive their OOAs in a timely manner or to direct patients towards resources that may be able to decrease their BOT, such as social work or support groups.

Policy

As individuals with cancer and multimorbid conditions have an increased burden of treatment, it may lead to increased adverse events and utilization of healthcare resources. This increased burden will lead to greater healthcare spending on the part of the patient and the system itself.[46-51] If the burden of treatment continues to afflict these individuals, acute care facilities must be able to management multiple disruptive conditions within an individual, on top of active cancer treatment. Having to manage cancer and other multimorbid conditions in an acute care setting has been shown to be difficult in stabilizing patient conditions and reducing readmission rates.[52-57] For this reason, policies should be enacted to provide resources for this population, in order to reduce the adverse events and resource use brought on by poorly managed conditions.

Looking specifically at individuals prescribed OOAs, this and future work may alter the process of patients acquiring their drugs. Manuscript two showed that patients waited on average 10 days to receive their drug. While this work did not examine each step of the process, previous work found that specialty pharmacy prescription processing and delivery accounted for the greatest number of days during the acquisition process.[34] Processing time at each step may need to be evaluated in order to shorten the acquisition time for patients. Additionally, policies may need to be adapting to assist cancer patients with multimorbid

conditions in reducing symptoms and modifications to OOA regimens. This may be clinics or hospital systems providing additional support for these individuals to help educate patients on proper self-management. Therefore, policies may be needed to force insurance companies to cover these additional services. Although they may bring about upfront costs, they may bring down costs in the long run for both patients and the healthcare system.

Manuscripts one and three focused on the increased burden of treatment experienced by individuals with cancer and multimorbid conditions. An increased number of multimorbid conditions led to increased burden of treatment, greater non-adherence, poor clinical outcomes, more treatment modifications, and worse overall health.[11-16,20,23-27] Another finding was that poor communication with providers was a primary concern for individuals.[13,20] Having cancer and multimorbid conditions often means multiple providers, which can be stressful for patients. Policies to provide more resources for patients to help decrease poor outcomes and improve provider communication, such as nurse navigators, would be beneficial to patients experiencing these issues. Policies to require and improve access across electronic health records (EHR) would help to improve communication and practice standards across patients' onolcogy providers and other specialists and PCPs. Additionally, policies to increase funding and coverage for the use of telehealth to provide patients with more access to providers and quality care may help to decrease patient stress and lead to better patient and clinical outcomes. The increase in telehealth would allow patients to access effective standards of care, proper discharge education and care, and easier access to prescription medications.

Conclusions

Burden of treatment is a relatively new concept, but it will continue to become even more vital as more individuals are required to manage multiple conditions. This dissertation focused on a population that must endure mental and physical struggle every day. This work filled a number of gaps within the literature, including: 1) providing a conceptual model for cancer patients with multimorbid conditions; 2) emphasizing the importance of patient perspective as a component of

BOT; 3) examining BOT within cancer patients with multimorbid conditions; 4) examining the impact of disease/treatment and healthcare system variables on the time to acquisition of OOAs; 5) examining the relationship between patient, social, disease/treatment, and healthcare system factors and temporary stoppages and how BOT might impact this relationship; and 6) providing evidence for continued new research and continued development of the concept of BOT, specifically within cancer patients with multimorbid conditions. This dissertation found that Individuals with cancer and multimorbid conditions are more likely to experience a greater BOT than this with cancer alone. Additionally, that certain patients may experience delays in receiving their OOAs, based on the type of insurance they have, the specific OOA drug they are prescribed, and whether or not they have an out-of-pocket cost. Finally, some patients may be more susceptible to experiencing temporary stoppages to their OOA regimens, based on sex and the specific OOA drug.

As the population life expectancy maintains the current rate and more individuals with cancer are actively managing other diseases, new research will be needed to empower these patients to overcome their burden and to effectively manage their diseases. The current literature is far behind the needs of this population. This work provided new insight to help address some of the gaps with the BOT literature. These gaps include examining BOT within cancer patients with multimorbid conditions; the challenges cancer patients experience in acquiring their OOAs; and how including examining BOT within cancer patient with multimorbid conditions and examining patient perspective, and examining how BOT might impact the relationship between patient's baseline characteristics and the modification of their OOA treatment regimen. The goals of this dissertation were to address these gaps and to build a foundation for a program of research that is focused on decreasing the burden of treatment within this population and allowing patients to take control of their cancer and multimorbid conditions.

REFERENCES

REFERENCES

1. Sikorskii A, Given CW, Given BA, et al. Do treatment patterns alter beliefs cancer patients hold regarding oral oncolytic agents? *Psycho-Oncology.* 2018;27(3):1005-1012.

2. Given B, Given CW, Sikorskii A, et al. Establishing mild, moderate, and severe scores for cancer-related symptoms: how consistent and clinically meaningful are interference-based severity cut-points? *Journal of Pain and Symptom Management.* 2008;35(2):126-135.

3. Tran VT, Barnes C, Montori VM, Falissard B, Ravaud P. Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions. *BMC Med.* 2015;13:115.

4. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med.* 2014;12:109.

5. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC Med.* 2012;10:68.

6. Eton DT, Elraiyah TA, Yost KJ, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. *Patient Related Outcome Measures.* 2013;4:7-20.

7. Eton DT, Ridgeway JL, Egginton JS, et al. Finalizing a measurement framework for the burden of treatment in complex patients with chronic conditions. *Patient Related Outcome Measures.* 2015;6:117-126.

8. Sav A, King MA, Whitty JA, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. *Health Expectations: An International Journal of Public Participation in Health Care and Health Policy.* 2013;18(3):312-324.

9. Rodgers BL. *Concept development in Nursing: Foundations, Techniques, and Applications.* 2nd ed. Philadelphia, PA: Saunders; 2000.

10. Antczak C, Trinh VQ, Sood A, et al. The health care burden of skeletal related events in patients with renal cell carcinoma and bone metastasis. *The Journal of Urology.* 2014;191(6):1678-1684.

11. Baz R, Lin HM, Hui AM, et al. Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on health-related quality of life. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer.* 2015;23(9):2789-2797.

12. Gershon AS, Mecredy GC, Guan J, Victor JC, Goldstein R, To T. Quantifying comorbidity in individuals with COPD: a population study. *The European Respiratory Journal.* 2015;45(1):51-59.

13. Gheihman G, Zimmermann C, Deckert A, et al. Depression and hopelessness in patients with acute leukemia: the psychological impact of an acute and life-threatening disorder. *Psycho-Oncology.* 2016;25(8):979-989.

14. Guy GP, Yabroff KR, Ekwueme DU, Rim SH, Li R, Richardson LC. Economic Burden of Chronic Conditions Among Survivors of Cancer in the United States. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2017;35(18):2053-2061.

15. Hart PA, Law RJ, Frank RD, et al. Impact of diabetes mellitus on clinical outcomes in patients undergoing surgical resection for pancreatic cancer: a retrospective, cohort study. *The American Journal of Gastroenterology.* 2014;109(9):1484-1492.

16. Hawkins NA, Soman A, Buchanan Lunsford N, Leadbetter S, Rodriguez JL. Use of Medications for Treating Anxiety and Depression in Cancer Survivors in the United States. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2017;35(1):78-85.

17. Huang BZ, Camp MS. Burden of preoperative cardiovascular disease risk factors on breast cancer surgery outcomes. *Journal of Surgical Oncology.* 2016;114(2):144-149.

18. Islam MM, Yen L, Valderas JM, McRae IS. Out-of-pocket expenditure by Australian seniors with chronic disease: the effect of specific diseases and morbidity clusters. *BMC Public Health.* 2014;14:1008.

19. Jim HSL, Sutton SK, Jacobsen PB, Martin PJ, Flowers ME, Lee SJ. Risk factors for depression and fatigue among survivors of hematopoietic cell transplantation. *Cancer.* 2016;122(8):1290-1297.

20. Kayser K, DeMarco RF, Stokes C, DeSanto-Madeya S, Higgins PC. Delivering palliative care to patients and caregivers in inner-city communities: challenges and opportunities. *Palliative & Supportive Care.* 2014;12(5):369-378.

21. Kleeff J, Costello E, Jackson R, et al. The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. *British Journal of Cancer.* 2016;115(7):887-894.

22. Maeda T, Babazono A, Nishi T, Miyazaki H, Tamaki K, Fujii M. The effect of diabetes with pharmacotherapy for breast cancer on care resource use. *Journal of Cancer Research and Therapeutics.* 2016;12(2):876-880.

23. Neugut AI, Zhong X, Wright JD, Accordino M, Yang J, Hershman DL. Nonadherence to Medications for Chronic Conditions and Nonadherence to Adjuvant Hormonal Therapy in Women With Breast Cancer. *JAMA Oncology.* 2016;2(10):1326-1332.

24. Østgård LS, Nørgaard JM, Sengeløv H, et al. Comorbidity and performance status in acute myeloid leukemia patients: a nation-wide population-based cohort study. *Leukemia.* 2015;29(3):548-555.

25. Presley CJ, Soulos PR, Tinetti M, Montori VM, Yu JB, Gross CP. Treatment Burden of Medicare Beneficiaries With Stage I Non–Small-Cell Lung Cancer. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2016:Jop2016014100.

26. Ritchie CS, Zhao F, Patel K, et al. Association between patients' perception of the comorbidity burden and symptoms in outpatients with common solid tumors. *Cancer.* 2017;123(19):3835-3842.

27. Sarfati D, Gurney J, Stanley J, Koea J. A retrospective cohort study of patients with stomach and liver cancers: the impact of comorbidity and ethnicity on cancer care and outcomes. *BMC Cancer.* 2014;14:821.

28. Thekdi SM, Milbury K, Spelman A, et al. Posttraumatic stress and depressive symptoms in renal cell carcinoma: Association with quality of life and utility of single-item distress screening. *Psycho-Oncology.* 2015;24(11):1477-1484.

29. Chaudhary RK, Bhaduri D, Bhatia M, Hatti S, Ba R, Meva J. Influence of comorbidity in cancer surgery on treatment decisions, postoperative course and oncological outcome. *Asia-Pacific Journal of Clinical Oncology.* 2013;9(1):47-52.

30. Dowling EC, Chawla N, Forsythe LP, et al. Lost productivity and burden of illness in cancer survivors with and without other chronic conditions. *Cancer.* 2013;119(18):3393-3401.

31. McLean S, Sheehy-Skeffington B, O'Leary N, O'Gorman A. Pharmacological management of co-morbid conditions at the end of life: is less more? *Irish journal of Medical Science.* 2013;182(1):107-112.

32. Ording AG, Horváth-Puhó E, Lash TL, et al. Prostate cancer, comorbidity, and the risk of venous thromboembolism: A cohort study of 44,035 Danish prostate cancer patients, 1995-2011. *Cancer.* 2015;121(20):3692-3699.

33. Dusetzina SB, Huskamp HA, Winn AN, Basch E, Keating NL. Out-of-Pocket and Health Care Spending Changes for Patients Using Orally Administered Anticancer Therapy After Adoption of State Parity Laws. *JAMA Oncology.* 2017;4(6).

34. Niccolai JL, Roman DL, Julius JM, Nadour RW. Potential Obstacles in the Acquisition of Oral Anticancer Medications. *Journal of Oncology Practice / American Society of Clinical Oncology.* 2017;13(1):e29-e36.

35. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. *The Annals of Pharmacotherapy.* 2004;38(9):1369-1376.

36. Cheng AC, Levy MA. Data Driven Approach to Burden of Treatment Measurement: A Study of Patients with Breast Cancer. *AMIA Annual Symposium Proceedings AMIA Symposium.* 2016;2016:1756-1763.

37. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer.* 2008;16(7):791-801.

38. Seal BS, Anderson S, Shermock KM. Factors Associated with Adherence Rates for Oral and Intravenous Anticancer Therapy in Commercially Insured Patients with Metastatic Colon Cancer. *Journal of Managed Care & Specialty Pharmacy.* 2016;22(3):227-235.

39. ACS. *Cancer Facts and Figures, 2018.* Cancer.org: American Cancer Society 2018.

40. Friedman AJ, Cosby R, Boyko S, Hatton-Bauer J, Turnbull G. Effective teaching strategies and methods of delivery for patient education: a systematic review and practice guideline recommendations. *Journal of Cancer Education: The Official Journal of the American Association for Cancer Education.* 2011;26(1):12-21.

41. Labrunee M, Pathak A, Loscos M, Coudeyre E, Casillas JM, Gremeaux V. Therapeutic education in cardiovascular diseases: state of the art and perspectives. *Annals of Physical and Rehabilitation Medicine.* 2012;55(5):322-341.

42. McGowan PT. Self-management education and support in chronic disease management. *Primary Care.* 2012;39(2):307-325.

43. Grady PA, Gough LL. Self-management: a comprehensive approach to management of chronic conditions. *American Journal of Public Health.* 2014;104(8):e25-31.

44. Lorig K, Laurent DD, Plant K, Krishnan E, Ritter PL. The components of action planning and their associations with behavior and health outcomes. *Chronic Illness.* 2014;10(1):50-59.

45. Lovell MR, Luckett T, Boyle FM, Phillips J, Agar M, Davidson PM. Patient education, coaching, and self-management for cancer pain. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2014;32(16):1712-1720.

46. Thorpe KE, Philyaw M. The medicalization of chronic disease and costs. *Annual Review of Public Health.* 2012;33:409-423.

47. Collaboration P-T. Optimizing chronic disease management mega-analysis: economic evaluation. *Ontario Health Technology Assessment Series.* 2013;13(13):1-148.

48. Erdem E, Prada SI, Haffer SC. Medicare payments: how much do chronic conditions matter? *Medicare & Medicaid Research Review.* 2013;3(2).

49. van Boven JF, Stuurman-Bieze AG, Hiddink EG, Postma MJ, Vegter S. Medication monitoring and optimization: a targeted pharmacist program for effective and cost-effective improvement of chronic therapy adherence. *Journal of Managed Care & Specialty Pharmacy.* 2014;20(8):786-792.

50. Brown PM, Gonzalez M, Dhaul RS. Cost of chronic disease in California: estimates at the county level. *Journal of Public Health Management and Practice : JPHMP.* 2015;21(1):E10-19.

51. Sambamoorthi U, Tan X, Deb A. Multiple chronic conditions and healthcare costs among adults. *Expert Review of Pharmacoeconomics & Outcomes Research.* 2015;15(5):823-832.

52. Schoonover H, Corbett CF, Weeks DL, Willson MN, Setter SM. Predicting potential postdischarge adverse drug events and 30-day unplanned hospital readmissions from medication regimen complexity. *Journal of Patient Safety.* 2014;10(4):186-191.

53. Willson MN, Greer CL, Weeks DL. Medication regimen complexity and hospital readmission for an adverse drug event. *The Annals of Pharmacotherapy.* 2014;48(1):26-32.

54. Wimmer BC, Dent E, Bell JS, et al. Medication Regimen Complexity and Unplanned Hospital Readmissions in Older People. *The Annals of Pharmacotherapy.* 2014;48(9):1120-1128.

55. Abou-Karam N, Bradford C, Lor KB, Barnett M, Ha M, Rizos A. Medication regimen complexity and readmissions after hospitalization for heart failure, acute myocardial infarction, pneumonia, and chronic obstructive pulmonary disease. *SAGE Open Medicine.* 2016;4:2050312116632426.

56. Olson CH, Dey S, Kumar V, Monsen KA, Westra BL. Clustering of elderly patient subgroups to identify medication-related readmission risks. *International journal of medical informatics.* 2016;85(1):43-52.

57. Yam FK, Lew T, Eraly SA, Lin HW, Hirsch JD, Devor M. Changes in medication regimen complexity and the risk for 90-day hospital readmission and/or emergency department visits in U.S. Veterans with heart failure. *Research in Social & Administrative Pharmacy : RSAP.* 2016;12(5):713-721.