Title: A randomized longitudinal intervention study to assess the efficacy and feasibility of telehealth-based strategies to increase oral chemotherapeutic agent medication adherence and health literacy among cancer patients in rural Eastern North Carolina.

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Merck Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	A randomized longitudinal intervention study to assess the efficacy and feasibility of telehealth-based strategies to increase oral chemotherapeutic agent medication adherence and health literacy among cancer patients in rural Eastern North Carolina.
Request Date:	May 18, 2015
Institution Name	East Carolina University
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	Objectives Objective 1: To assess the barriers to, and facilitators of, adherence to oral chemotherapeutic agents among cancer patients who are at high-risk of non-adherence. Objective 2: To test the effectiveness of two telehealth adherence motivation strategies among cancer patients on oral chemotherapeutic agents who are at high-risk of non-adherence. Hypothesis: H_1: Intervention groups will have increased medication adherence rates compared to control group H_2: Intervention groups will have increased health literacy and self-efficacy rates compared to control group
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	The World Health Organization has estimated that globally, only 50% of patients take their medications as prescribed[1] and in the United States, 3 out of 4 Americans report not taking their medications as directed.[2] Although lack of medication adherence affects all people, those with long-term chronic illnesses, such as cancer patients, have lower medication adherence rates as compared to patients with acute conditions.[3-4] Oral chemotherapeutic agents (OCAs), including targeted therapies, are often prescribed to cancer patients during treatment to reduce tumor size, burden of disease, and increase overall survival.[5] Although OCAs are increasingly being used and are commonly preferred by patients,[5-8] adherence varies with compliance rates as low as 16% and as high as 100%.[9-10] Additionally, adherence to OCAs is lower than adherence to intravenous chemotherapy.[11] There are many reasons for non-adherence including side-effects, treatment costs, confusion of treatment instructions, inadequate social support, problems remembering, poor clinician/patient communication, low health literacy, and other psycho-social issues of patients.[5,12-19] Cancer patients who adhere to their OCA regimens have a greater chance of cancer eradication, non-recurrence, long-term quality of life[1], as well as reduced hospital utilization and decreased health care costs.[8,20] Thus, it is critical to develop and test interventions that effectively improve adherence to OCAs. Literature in this area is limited and has been criticized for not demonstrating significant effects on adherence behavior and for having low methodological quality.[21-25] Furthermore, a recent systematic review found that a quantitative measure of adherence to OCAs was only reported in 4% of published clinical trials.[26] **This study will address some of these issues by conducting a theoretically driven randomized controlled trial using multi-method adherence strategies and quantitative adherence measurements across multiple points in time.** Although the OCA medication adherence literature is limited and has methodological issues, some components of interventions in other medication adherence literature has shown promising results. Electronic monitored adherence feedback and cognitive-

educational components were the only intervention approaches that had a significant effect on increased medication adherence per a systematic review and meta-analysis of medication adherence literature among drug dosing studies.[27] Studies have also demonstrated that a strong patient-provider relationship that includes trust, consistency, and continued interaction, is a critical factor in a patient's adherence behavior.[28-29] Furthermore, nurse-based interventions, including nurse-coach approaches, have significantly impacted adherence.[30-33] Although these approaches have shown promise in increasing adherence, they are not always sustainable unless made cost-effective and translated into health care practices. Technology-based strategies in health care or telehealth have also started to play an important role as healthcare systems move away from the traditional fee for service system and towards new models of care. Thus, telehealth can potentially transition these evidence-based approaches into sustainable solutions. These technologies are becoming less expensive and more widely available and consequently can be adopted easier than ever before. The use of technologies for chronic disease care management has been associated with increased medication adherence, cost reductions, improvement in some physiologic measures, and high rates of satisfaction.[47] **We propose to unify components of these effective approaches in a novel way**. **We hypothesize that using technology-based strategies coupled with a tailored nurse coach approach, that includes a cognitive education intervention with a strong patient-provider communication component, will effectively increase medication adherence for our patient population.** Evidence-based strategies for leveraging these technologies to improve health outcomes and behavior such as medication adherence will be extremely important in this changing healthcare environment. Given the critical role that effective patient-provider communication and patient-centered strategies play, technology should not be seen as a barrier, but rather a facilitator that provides a platform for sustainable and cost-effective evidence-based approaches for increased medication adherence.

We propose to assess the efficacy and feasibility of two combined telehealth-based strategies (electronic medication-event monitoring and tailored nurse coach) in an effort increase OCA adherence and health literacy among cancer patients in rural Eastern North Carolina (ENC). With strong support from our collaborators at Vidant Medical Center and Leo W. Jenkins Cancer Center, study participants will include cancer patients that are within their first two cycles of a new oral chemotherapy regimen at Vidant Medical Center/Leo W. Jenkins Cancer Center, which serves individuals throughout the 29 counties in rural ENC. Patients at Leo W. Jenkins Cancer Center/ Vidant Medical Center are susceptible to barriers such as low literacy, transportation barriers, lack of social support, financial barriers, and many other factors that can affect their cancer care experience. *These factors alone make this population at high-risk for non-adherence to their OCAs regimen.* Vidant Health is the largest health care system in North Carolina, serving 1.4 million people. The Administrator of Cancer Services for Vidant Health, Phyllis DeAntonio and the Coordinator of the VHCNP, Judy Koutlas, are Co-Investigators on this study and have provided assurances concerning patient access, recruitment, and retention. This innovative and exploratory study can have a transformative impact on patient-centered cancer care and ultimately can improve the overall survival and quality of life of cancer patients.

2.3 Study Design	**Objective 1. To assess the barriers to, and facilitators of, adherence to oral chemotherapeutic agents among cancer patients who are at high-risk of non-adherence.** Leo W. Jenkins Cancer Center/ Vidant Medical Center serves cancer patients throughout the 29 counties of ENC. Using the three-stage process of elicitation, intervention, and evaluation, we will assess factors that influence non-adherence among this population. This formative qualitative assessment will be accomplished by conducting interviews/focus groups with English speaking cancer patients (n=25-30) and through key informant interviews with clinicians (n=17). Interviews/focus groups will include a cognitive interviewing component where we will ask patients to explain their OCA treatment plan in their own words, including their understanding of side effects/drug interactions. Comparative content analysis will be conducted using a written version of their treatment plan. We will also conduct key-informant interviews with all cancer care navigators (n=12), a sample of oncologists (n=4), and the oncology pharmacist at Leo W. Jenkins Cancer Center's Outpatient Pharmacy. Specific aim 1 will act as a baseline assessment to identify the unique factors that contribute to non-adherence and will directly inform the development of tailored medication adherence strategies outlined in specific aim 2. **Objective 2. To test the effectiveness of two telehealth adherence motivation strategies among cancer patients on oral chemotherapeutic agents who are at high-risk of non-adherence.** We are proposing a randomized multi-arm intervention study of 150 subjects with two intervention arms and a control arm (50 subjects per arm). Subjects will be stratified by cancer and then randomized into each of the three groups. The Information-Motivation-Behavioral Skills Model of Adherence and the results of specific aim 1 will guide this aim. Intervention Arm 1 will receive a Medication Event Monitoring System (MEMS) with feedback. Intervention Arm 2 will receive the MEMS plus a tailored nurse coaching component. Controls will receive standard-of-care from the Cancer Center. Specifically, we want to test whether a tailored nurse coaching intervention component will significantly improve medication adherence at higher rates as compared to the MEMS alone. The MEMS is a cap that is equipped with a microchip that registers the date and time of each cap opening (dosing history). MEMS caps will be given to patients in intervention Arms 1 and 2 either in clinic or it will be mailed to them. MEMS caps will only be provided to those who are taking a medication that comes in a bottle. Patients who receive their medication in blister packs will not be given a MEMS cap (as we do not think it's a good idea for patients to transfer medication from blister packs to bottles). If medications patients are taking come in a bottle, Leo Jenkins pharmacy has agreed to fill Arm 1 and 2 oral chemotherapy prescriptions into a bottle that fits the MEMS cap. If patients in Arms 1 and 2 have two or more oral chemotherapy agents they are taking, they will be instructed to use the MEMS cap with the medication they take most frequently. Currently, there is no gold standard for measure of medication adherence but the MEMS device has been demonstrated to be a valid and objective method to assess medication adherence.[14-15] The nurse coach intervention component will involve an individualized barriers/facilitators screening tool and regular contact with cancer patients via telephone calls across a six-month

	period. We hypothesize that although both telehealth strategies will be effective at increasing medication adherence, Arm 2 will have a significantly greater effect on adherence. This hypothesis is supported by existing medication adherence literature that suggests a tailored intervention using multiple adherence strategies can potentially have a significant impact on increasing medication adherence.[16] Together, these two fundamentally linked aims will test innovative approaches that will help us understand what type of intervention may deliver the biggest impact in medication adherence to OCAs for cancer patients. Most importantly, developing and implementing evidence-based strategies for medication adherence can ultimately improve the overall survival and life expectancy of cancer patients.
2.4 Study Flowchart	See attached project timeline and recruitment timeline in Appendix A & B, respectively
2.5 Study Procedures	The Information-Motivation-Behavioral Skills Model of Adherence (IMB model) will guide the proposed study. This model posits that adherence information, adherence motivation, and adherence behavioral skills are empirically linked to adherence behavior which ultimately impacts health outcomes. One important aspect of the IMB model is that it takes into account external moderating factors that can influence the relationship between IMB model constructs and adherence behavior.[42] The IMB model of adherence is based on a validated generalized IMB approach to understanding and promoting health behavior and has been used extensively in research concerning HIV-related behaviors (i.e. prevention and adherence), diabetes self-care, and condom use among high-risk populations.[42-45] At its core, the IMB model theorizes that adherence-related information, motivation, and behavioral skills are fundamental determinants of adherence. Therefore, if individuals are well informed, motivated to act, and acquire needed adherence behavioral skills, they can effectively increase their adherence behavior.[43-44] The intervention in this study will use two evidence-based telehealth strategies for improving adherence, while examining mediating and moderating factors that may influence adherence to OCAs in an effort to understand the underlining mechanism/s for an effective intervention. Mediating factors include *Adherence Information, Adherence Motivation,* and *Adherence Behavioral Skills (see Table 1 in Appendix)*. Moderating factors include access to medical care and insurance status, stigma of cancer, psychological health (i.e. depression), rurality-related and quality of life factors. Using the three-stage process of elicitation, intervention, and evaluation, this study will consist of a formative research phase in which an assessment of the population of interest' initial levels of adherence will be conducted, comprehension of treatment plan, and an assessment of facilitators and barriers to medication adherence relevant to both mediating and moderating factors. This formative research phase will inform a tailored adaptation of the IMB model for the population of interest to remediate identified adherence-related information, motivation, and behavioral skills deficits and moderators that can be modified to influence adherence behavior. Finally, we will evaluate the tailored adherence strategies guided by the IMB model using multi-model outcome data (Table 2) expected to be influenced by improved adherence behavior. **Objective 1. To assess the barriers to and facilitators of adherence to oral chemotherapeutic agents among cancer patients who are at high-risk of non-**

adherence.

Overview: Poor medication adherence encompasses more than patients not taking their medicines as directed.[47] The National Council on Patient Education provided a comprehensive overview of factors that contribute to poor adherence, which include medication-, patient-, prescriber-, pharmacy-related factors. Compounding these issues is low health literacy and transportation barriers that affect timely access to follow-up care which are prominent issues among rural populations. This study will conduct a baseline qualitative assessment to identify and understand the unique factors that contribute to non-adherence, which will inform a tailored approach of adherence strategies that specifically address the needs of our population of interest.

Population of Interest: ENC serves a large geographic area of NC that includes 29 of the 100 counties in NC. The NC Department of Commerce annually ranks counties based on economic well-being and assigns each a tier designation (Tier 1, most economically distressed through Tier 3, least economically distressed). Overall, ENC counties comprise approximately 38% of all Tier 1 counties, the most economically distressed counties in the state. Vidant Health is the largest health care system in NC serving the ENC region, and has been accredited by the American College of Surgeons Commission on Cancer since 1991, as well as a designated as an Academic Comprehensive Cancer Program.

***Recruitment Strategy*:** Participants for this aim will be recruited from Leo W. Jenkins Cancer Center. Maximum variation sampling will be used to select participants to provide a representative sample for conducting needed preliminary assessments. Navigators will identify, contact, and refer cancer patients for this formative research phase. Qualitative assessments (i.e. interviews focus groups) will be conducted with 25-30 English speaking cancer patients who are currently undergoing or have recently completed (within 3 months) an OCA regimen to understand their barriers to and facilitators of adherence. In addition to the patient's themselves, key-informant interviews will be conducted with all cancer care navigators (n=12), a sample of oncologists (n=4), and the oncology pharmacist. Co-investigators, Koutlas and DeAntonio, will assist in recruitment and coordination of interviews.

Research Design: *First*, qualitative assessments (i.e. interviews/focus groups) will last approximately one hour and will be held at Leo Jenkins Cancer Center or Vidant Medical Center during the cancer patient's scheduled follow up appointments with their oncology team. Participants will provide written informed consent prior to the interview/focus group discussions. Participants will receive a small monetary incentive for their participation ($50 gas card). A panel of experts (including faculty from health education and public health, oncologists, cancer nurse navigators, and cancer care team) will inform the topical guide used in these assessments. Topical guide questions will include questions regarding illness experiences (symptoms/side effects, complexity of regimen), interactions with others, caregiver availability, informational resources, cognitive processes, and mood state. Data gathered from these discussions will help identify the origins of non-adherence and will inform the intervention components of specific aim 2. Both surface and deep structure adaptation will take place in an effort to make instruments and interventions culturally and linguistically relevant as well as understanding our population's core cultural values, preferences, and medically related needs.[49]

	Second, we will conduct in-person cognitive interviews with cancer patients by asking patients to explain their OCA treatment plan in their own words, including their understanding of side effects/drug interactions.[50] The purpose is to investigate how patients interpreted their respective treatment plans and to document the nature of misunderstandings that may contribute to non-adherence. From a health literacy perspective, we hypothesize that misunderstanding may be the result of patient literacy limitations, complexity of treatment plans, and the lack of information provided regarding potential side-effects, drug interactions, adherence expectations, and how to address missed or delayed doses. Comparative content analysis will be conducted using a written version of the patient's prescribed treatment plan provided by their oncologist. *Last*, we will conduct key-informant interviews with all cancer care navigators from Leo W. Jenkins Cancer Center (n=12), a sample of oncologists who treat patients at Leo W. Jenkins Cancer Center (n=4), and the oncology pharmacist at Leo W. Jenkins Cancer Center's Outpatient Pharmacy. These qualitative interviews will provide an in-depth understanding, from the provider's perspective, regarding the unique challenges in working with patients who are at high-risk for non-adherence and will identify the structural factors that might influence sub-optimal adherence among this population. Additionally, it will provide a preliminary understanding of the functional definition of adherence for cancer patients at the Cancer Centers and acceptable levels of medication adherence among health care providers. This data will inform the development of tailored adherence strategies for increased medication adherence, guided by the IMB model, outlined in specific aim 2. As part of specific aim 1, we will assess health literacy. Low literacy has been associated with a lack of knowledge about a disease process and poor self-management skills in patients with chronic disease.[50] Furthermore, marginal functional literacy has been associated with poor physical health, psychological health, and higher health care costs.[50] The implication for medication adherence is the inability to read, understand, and act on health information and medication use. We will assess baseline health literacy using the Rapid Estimate of Adult Literacy in Medicine Short Form[50] to inform the development of a linguistically appropriate tailored adherence intervention. ***Data Analysis:*** All qualitative assessments will be audio-recorded, transcribed verbatim and analyzed using qualitative analysis techniques. Open, axial, and selective coding will allow for data reduction and categorization of data into themes. Analytic memos will be written and kept throughout the coding process. In order to check for coding consistency, trustworthy or consistency checks will be employed. The coding process will be an iterative one and will be conducted by a team of two qualitative researchers. ***Feasibility:*** The study's co-investigators are active partners in the study and will be facilitating access to the identified populations of interest for specific aim 1. The collaborative nature of this proposal will provide outcomes that can potentially improve the efficacy of services provided via the Leo W. Jenkins Cancer Center/ Vidant Medical Center and medical adherence among cancer patients. There is a strong commitment from Vidant Medical Center in the development, implementation, and evaluation of this proposed study. Drs. Richman and Torres have extensive qualitative research experience. Specifically, they have worked with hard-to-reach and medically underserved populations, in both rural and urban settings, and have experience in

topical guide development, study recruitment, conducting the proposed qualitative assessment, transcription, and analysis.

Expected Outcomes: Specific Aim 1: Given our rural ENC population, we hypothesize that low health literacy, confusion of treatment regimen and potential side-effects, timely access to prescribed treatment, poor patient-provider communication, misguided perceptions of adherence, and not remembering may be barriers to adherence. Facilitators may include adherence education, self-efficacy, affect support, and reminder systems.

Objective 2. To test the effectiveness of two telehealth adherence motivation strategies among cancer patients on oral chemotherapeutic therapy agents who are at high-risk of non-adherence.

Overview: We are proposing a randomized multi-arm intervention study (n=150) with two intervention arms and a control arm. The IMB model and the results of specific aim 1 will guide this aim. Intervention Arm 1 will receive a Medication Event Monitoring System (MEMS) with feedback. Intervention Arm 2 will receive the MEMS plus a tailored nurse coach component. Controls will receive standard-of-care from their Cancer Center. Specifically, we want to test whether a tailored nurse coaching intervention component will significantly improve medication adherence at higher rates as compared to MEMS alone. The MEMS is a medication bottle with a cap that is equipped with a microchip that registers the date and time of each cap opening (dosing history). Currently, there is no gold standard for measure of medication adherence but the MEMS device has been demonstrated to be a valid and objective method to assess medication adherence.[51-52] The nurse coach intervention component will involve an individualized barriers/facilitators screening tool and regular contact with cancer patients via telephone calls across a six-month period. We hypothesize that although both telehealth strategies will be effective at increasing medication adherence, Arm 2 will have a significantly greater effect on adherence. This hypothesis is supported by existing medication adherence literature that suggests a tailored intervention using multiple adherence strategies can potentially have a significant impact on increasing medication adherence.[47]

Population of Interest: Participants for specific aim 2 will be recruited from Vidant Medical Center/Leo W. Jenkins Cancer Center. Eligibility criteria includes patients who are starting a new cycle of OCAs (recruitment will happen within their first two cycles), ambulatory, age 18 years or older, able to consent for self, able to understand and speak English, and have a cellphone or landline. In addition, since this intervention uses telehealth approaches, participants must be able to understand and willing to use the MEMS devices. Exclusion criteria includes life expectancy <3 months as determined by oncologist, current participation in a similar study or in investigational drug trials where adverse effects have not been fully elucidated, ~~patients who are on simultaneous oral and IV chemotherapeutic regimens,~~ and presence of significant psychiatric or cognitive impairments as determined by oncologists and study team.

Recruitment Procedures: On a daily basis, the study team (i.e. LJCC clinical trial nurses) will discuss with the nurses and oncologists from Leo W. Jenkins Cancer Center (LJCC) about potential cancer patients who started a new cycle of OCAs and who are potentially eligible for participation in this study. The nurse coach or research assistants will provide a recruitment flyer about the study to potential participants when the patient is in the clinic or hospital. If the patient provides consent, a member from

the study team can initiate the enrollment visit concurrently or can contact patients by phone to set up an initial enrollment visit within two weeks. At enrollment, written informed consent will be obtained and baseline assessments will be administered to all participants. Randomization to Arm 1, Arm 2, or Control Arm will also occur at enrollment. All study materials and procedures will be approved by the East Carolina University and Medical Center Institutional Review Board.

Intervention Design:

Control Group (Standard-of-Care). Subjects assigned to the control arm will receive standard-of-care at Vidant Medical Center and Leo W. Jenkins Cancer Center, which includes education on treatment plan provided by a medical oncologist, clinical pharmacist, and/or nurse, follow-up by a nurse navigator, and patient education information packets included in the product information from the drug manufacturer.

Lite Group (Arm 1: MEMS). Subjects randomized to the *lite group* will receive a Medication Event Monitoring System (MEMS) device with feedback. Subjects will be advised to only open their pill bottles when they take their medications. Patients will also be given a MEMS diary to record unscheduled cap openings, such as those to refill the bottle, so that those unscheduled events unrelated to adherence can be removed from analysis. Currently, there is no gold standard measure of medication adherence, but the MEMs has been used extensively in medication adherence studies.[54-55] Furthermore, it has been shown that drug package opening times is a strong indicator of the actual time a person takes a dose of medication.[38-40] Participants will meet with the nurse coach during their regularly scheduled monthly oncology visits where the MEMS data will be collected. During this monthly meeting, participants in the *lite group* will receive feedback of their medication-taking behavior via a MEMS report. The nurse coach will explain to the participant how to interpret the feedback report. The purpose of this feedback is to give participants insight into their own medication-taking behavior, and assess if this type of feedback alone can increase their self-efficacy and improve medication adherence and health outcomes.

Enhanced Group (Arm 2: MEMS + Nurse Coach). Subjects randomized to the *enhanced group* will receive the MEMS outlined in Arm 1, plus a tailored nurse coach component. Before beginning their OCA regimen, patients in Arm 2 will be administered a barriers/facilitators screening tool (adapted from Schneider et al[5]., and informed by IMB model/specific aim 1) that will help the nurse coach identify specific adherence strategies (i.e. cognitive education, knowledge skills, and affective support) tailored to the participant's needs. Once a tailored intervention plan is developed, participants will receive a 60-minute session conducted by the nurse coach. The educational component will include: information about the patient's cancer treatment, why it was selected, and expected outcomes; clear instructions about medication dosing schedule; what to do if a dose is missed or delayed; medication side effects and/or potential drug interactions; addressing adherence-related heuristics; and a self-developed glossary of terms associated with the OCA regimen (translating difficult medical terminology into meaningful "patient-language"). The behavioral skills and affective support strategies include coping strategies for side effects, skills for fitting medication regimen into daily routine (i.e. cues and medication plan), identifying a support network, communication skills for interacting with providers, and facilitating a positive perception of a positive self-management experience. Patients will receive weekly phone calls from the nurse coach during the first month of the intervention, and

then bi-monthly follow-up calls for the remainder of treatment or 6-month follow-up period (whichever occurs first). During these calls, lasting 15-20 minutes, the nurse coach will assess adherence strategies, evaluate for effectiveness, and modify or reinforce as needed. During monthly face-to-face meetings, participants in the *enhanced group* will also receive feedback of their medication-taking behavior from the MEMS. MEMS feedback will be used to show patients their own medication-taking behavior via the MEMS Report, to correct any misperceptions of actual adherence and to identify problem areas. The nurse coach will modify the intervention plan to address identified barriers to adherence at this time.

2.6 Study Duration

2 years; Start: September 1, 2015 End: August 31, 2017

2.7 Statistical Analysis and Sample Size Justification

Table 2. Outcome Measures	Data Collection Instrument	Expected Outcomes
Primary Outcome Measures		
Self-report medication adherence	Ask-20	H_1: Arm 1 and Arm 2 will have increased self-report adherence rates compared to control group H_2: Arm 2 will have significantly higher rates of self-report medical adherence compared to Arm 1 and Control group
Non-self-report measures of adherence 1. Dosing History 2. Pill count 3. Pharmacy refill rates 4. Missed Medical Appointments	1. EM-feedback: MEMS Data 2. Pill count: This will be conducted in-person by nurse coach 3. Pharmacy refill rates: Secondary Data from Electronic Medical Record 4. Secondary Data from Electronic Medical Record	H_1:Arm 1 and Arm 2 will have increased non-self-report adherence rates compared to control group H_2: Arm 2 will have significantly higher rates of medical adherence compared to Arm 1 and Control group
Self-Efficacy	Self-Efficacy for Appropriate Medication Use Scale(SEAMS) (pre/post)	H_1: Arm 2 will have significantly higher rates of self-efficacy compared to Arm 1 and Control group
Health Literacy	CHLT-30 REALM-R	H_1: Arm 2 will have significantly higher health literacy level compared to Arm 1 and Control group
Secondary Outcome Measures		
Usability and Satisfaction	1. Satisfaction with nurse coach components 2. Usability of MEMs for medication adherence	H_1: Arm 2 will have significantly higher satisfaction level compared to Arm 1 and Control group
Hospital Utilization (i.e. ER visits, hospitalizations, and length of stay)	Secondary Data from Electronic Medical Record	H_1: Arm 1 and Arm 2 will report lower hospital utilization rates compared to control group

We will also assess health outcomes/treatment response via results from routine diagnostic testing (e.g. CT, MRI, PET, bone scan, bone marrow aspiration and biopsy, tumor marker), as per oncologist for participants enrolled in this study. Co-investigators have agreed to assist with the interpretation of diagnostic test results. We expect diagnostic results to be affected by adherence behavior.

Description of Assessments Tools:

Ask-20 Tool: This is a validated tool that may be a useful brief measure of adherence behavior and barriers to treatment adherence (Matza et al., 2009).

Cancer Health Literacy along a Continuum (CHLT-30): The CHLT-30 is designed to measure cancer health literacy along a continuum. Accurate measurements of theoretical constructs such as cancer health literacy allow researchers to estimate

treatment effect in intervention studies, assess change over time, and establish relationships with theoretically relevant factors and clinically important outcomes (e.g., morbidity, mortality). The instrument has a broad content coverage, very high reliability, and is strongly linked to self-confidence about engaging in health decisions. The CHLT-30 is easy to administer and takes approximately 10–15 minutes. The test score is obtained by the total number of correct responses and ranges from 0 to 30.
Self-Efficacy for Appropriate Medication Use Scale(SEAMS): This is a validated 13-item self-report scale measuring patient confidence in the ability to take medications properly. The measure has high internal consistency and strong criterion-related validity.[19] This survey will be administered in-person by nurse coach at enrollment visit, and and final in-person meeting.
REALM-R: This is a shortened version of the REALM, which is used to help identify literacy levels of adult patients. It consists of 8 items, and is used to measure how well individuals can read words they will encounter in a medical setting.[59] This will be used as initial assessment of the level of health literacy during the formative research phase.

Sample Size Estimation. A sample size of 150 subjects, 50 in each arm (control, Arm 1, and Arm 2) is sufficient to detect a 10-point difference in mean medication adherence rates (measured by MEMS) between the three groups, assuming equal standard deviation of 16 using a two-tailed t- test of difference between means with 80% power and a 2-sided alpha of .05. Medication adherence rates in the literature vary based on the methods of measurement. The assumptions used in our sample size calculations are based on similar studies, especially those that used the MEMs device as the primary measure of medication adherence [4,6]. Participants will be followed up for a total of 6 months.

Statistical Analysis: A variety of bivariate statistical analyses will be utilized to examine the data collected from this study. Descriptive statistics and data visualizations will be used to assess both the overall distribution of important outcome variables as well as differences in distributions between treatment arms. Differences between treatment groups for pre/post changes in non-count quantitative outcomes (i.e. Morisky Medication Adherence Scale Scores, Self-Efficacy Scale, etc.) will be assessed using a combination of t-tests and ANOVA methods or nonparametric tests (Kruskal-Wallis and/or Wilcoxon tests) as appropriate for the collected data. Count based quantitative outcomes (number of ER visits, hospitalizations, days of stay) will be compared across groups using a mix of count regression models. In particular, Poisson regression will be used to compare treatment arms on standard count data outcomes. Alternatively, if the counts are found to be overdispersed (having higher than expected variance) then negative binomial regression will be utilized to compare treatment arms with an eye to accounting for the unexpectedly high variation in count outcome data. Categorical data (i.e. adherence counts and rates) will be analyzed with via contingency tables analysis utilization a mixture of Chi-Square tests and Fisher's exact tests as appropriate. All statistical analysis will be performed using a mixture of SPSS (version 21) and SAS Software (version 9.4).

2.8 Specific Drug Supply Requirements	We are not requesting any drug supplies for this project.
2.9 Adverse Experience Reporting	Participants will be told that they are free to leave the study at any time and can resume services at their respective cancer center/clinic with no penalty. If an adverse experience should be reported, we are required to notify our institutional review board (IRB). Then, the IRB will review the report and determine the appropriate action.
2.10 Itemized Study Budget	Our itemized study budget and justification appears in Appendix C.
2.11 References	1. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. *Eur J Cardiovasc Nurs. 2003; 2: 323.* 2. Cooke C. Take As Direction: A Prescription Not Followed. *National Community Pharmacists Association*. December 15, 2006. 3. Osterberg L, Blashcke T. Adherence to Medication. *N. Engl J Med.* 2005; 353:487-497. 4. U.S. Department of Health and Human Services. Medications and Older People. *FDA Consumer Magazine*. September-October 1997. Accessed February 18, 2015. 5. Schneider S, Adams D, Goddelin T. A Tailored Nurse Coaching Intervention for Oral Chemotherapy Adherence. *J Adv Pract Oncol*. 2014; 5(3): 163-173. 6. Weingart SN, Bach PB, Johnson SA, et la. NCCN Task Force Report: Oral Chemotherapy. *Journal of the National Comprehensive Cancer Network*. 2008; 6(3): 1-25. 7. Lio G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol*. 1997; 15(1): 110-115. 8. Twelves C, Gollins S, Grieve R, Samuel L. A randomized cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer. *Annals of Oncology*. 2006; 17(2): 239-245. 9. Ruddy K, Mayer E, Partridge A. Patient Adherence and Persistence with Oral Anticancer Treatment. *CA: A Cancer Journal for Clinicians*. 2009; 59(1): 56-66. 10. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to Therapy with Oral Antineoplastic Agents. *J Natl Cancer Inst*. 2002; 94(9): 652- 661. 11. Wood L. A review on adherence management in patients on oral cancer therapies. *J Oncol Nurs*. 2012; 16(4): 432-438. 12. 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. 13. Ngoh LN. Health literacy: A barrier to pharmacist-patient communication and medication adherence. *J Am Pharm Assoc*. 2009; *49*(5):32–146.

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2.12 Publication Plan	**Presentations at national scientific meetings:** It is expected that approximately 2-4 presentations at national meetings would be appropriate for a research study this size. Potential targeted scientific meetings for dissemination of results are the American

	Association for Cancer Research, American Association for Cancer Education, American Society of Clinical Oncology, American Public Health Association's annual meeting, Academy of Oncology Nurse & Patient Navigators annual conference, and Oncology Nursing Society's annual congress. PIs and Co-investigators are members of these professional organizations and will be active participants in presentations at these scientific meetings. **Dissemination with local oncology special interest groups:** This research team is an active participant in local efforts that promote best practices for cancer patients throughout the cancer care continuum. As such, we will disseminate study results and share study protocols, assessment tools, and intervention components developed during the course of this study to advance the translational nature, from theoretical to clinical practice, of this study. Local groups include North Carolina Oncology Navigation Association (NCONA), Eastern North Carolina Cancer Support Community, and Eastern North Carolina Cancer Coalition. **Dissemination via Vidant Health media outlets: In an effort to** advance the translational implications of study results into practice, our dissemination strategy will include consistent communication with the cancer care practice community at Vidant Health. This includes Vidant Medical Center's Cancer Committee, Vidant Medical Center's Cancer Annual Report that is made publically available via Vidant Health's website, and Vidant Health's Navigation meetings. **Dissemination via manuscripts:** Translation of research findings into practice in the health promotion sciences is important and will be accomplished by publishing results in high impact peer-reviewed journals that target audiences addressing the science that underpins clinical practice and is concerned with improving health outcomes throughout the cancer care continuum. Additionally, manuscripts will specifically focus on intervention reach, adoption, implementation, and maintenance that have been identified as critical areas that need to be better understood in order to address the gap between research and practice.
2.13 Curriculum Vitae	The curriculum vitae's for Dr. Richman and Dr. Torres appear in Appendix D.
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.