A Picture is Worth a Thousand Words:

A Randomized Controlled Trial to Assess the Impact of a Computerized Pictorial Medication Calendar

Medication Taking Behaviour

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AUTHOR'S DECLARATIONS

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

ABSTRACT

OBJECTIVES

The primary was to determine if a pictorial medication calendar would improve patient adherence to supportive medication regimens for adult patients receiving chemotherapy treatment. The secondary objectives were to: a) assess if the pictorial medication calendar would improve concordance with prescribed supportive care medication regimens, b) assess patient satisfaction associated with using the calendar and c) determine whether this tool affects participants' quality of life.

METHODS

Prospective, open-label, RCT with participants randomly assigned 1:1 to receive either routine care or routine care plus the intervention. Adherence was measured using pill count and diary. Concordance was measured by assessment of symptoms of nausea and vomiting in relation to PRN antiemetic use. Medication use and self-efficacy was evaluated using the MUSE scale. Participant satisfaction was evaluated using surveys created by the research team. A correlation analysis was performed between pills dispensed and taken as per the different adherence tools and a line of best fit was plotted where possible. A mean score difference was performed for the MUSE Scale results from baseline to end of study. A regression analysis was performed to determine if the symptoms of nausea and vomiting could predict the number of PRN anti-emetics taken. Data on participant satisfaction was analyzed graphically.

RESULTS

The correlation between scheduled pills dispensed and taken as per pill count was $p<0.001$, $r=0.96$. The correlation between scheduled pills dispensed and taken as per the diary was $p=0.015$ and $r=0.71$. The correlation between the PRN number of pills taken as per the pill count and average symptoms recorded in the diary was $r=0.65$ and $p=0.06$. The correlation between the number of PRN pills taken as per the diary and the average symptom score was $p=0.47$, $r= 0.28$ and between the PRN pills taken as per the diary and the number as per the pill count was $p=0.19$ and $r=0.49$. For the regression analysis model that assesses whether symptoms can predict PRN medication use in the intervention arm, $F(2,3)=7.24$, $r^2=0.8284$, adjusted $r^2=0.7141$, $p=0.035$. Due to the low number of participant data in the control arm, a regression analysis was not possible. The line of best fit for the intervention arm was $y=-0.09x+3.06$, $R^2 = 0.05$ and for the control arm, $y=1.11x+0.16$, $R^2 = 0.92$. For the intervention arm, the mean of score difference for the MUSE scale was 0.7, std. dev. = 4.40. For the control group arm the mean of the score difference of the MUSE scale was 1.86, std. dev.= 4.99. The alternative hypothesis, Ha: diff>0, where $Pr(T>t)= 0.67$, $t(15)= -0.46$ was chosen. Of the 17 participants for which results were available for the survey, 8 of the intervention group participants and 3 of the control group participants completely disagreed that the medication regimen was complicated, 1 participant in the intervention group and 2 in the control group moderately disagreed, none of the participants neither agreed nor disagreed, 1 in the intervention arm and 2 in the control arm moderately agreed and no participants completely agreed. Participants that received the calendar found it useful for medication taking behaviours. Approximately 80% of participants either moderately or completely agreed that the diary

helped keep track of medications, with which medications to take, when to take them and how many times per day.

DISCUSSION

There appeared to be a correlation between scheduled pills taken as per the pill count and as per the diary, however the correlation was not statistically significant. Participants in both arms tended to take the majority of all prescribed medications according to both pill count and diary. There appeared to be a trend towards predictability of PRN anti-emetic use with increased symptoms, however this trend was only visible with pill count and not with the ORN anti-emetic pills taken as per diary recording. The MUSE scale results between the intervention and control arm did not appear to be significantly different. Of the intervention arm participants who answered the questions related to the calendar, the majority either moderately or completely agreed that it was a useful tool. Therefore, at this point it cannot be assumed that medication use and self-efficacy is improved with the use of the calendar. Participants in the control arm found the treatment regimen less complicated overall. The pictorial medication calendar tool may have played a factor in this response as those in the intervention arm would have not only been given routine care, but also would have received further information from the pictorial medication calendar.

CONCLUSION

Therefore, it appeared that the calendar was a useful tool, subjectively to participants involved in the study for ease of medication use. Furthermore, it also appears that participants who received the diary felt that their regimen was less complex. However, at this point it cannot be stated that the tool significantly affects adherence in a statistically significant manner as further data collection is required.

Keywords: Patient adherence, chemotherapy, pictorial aid, complex medication regimen, cancer

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DEDICATION

To my husband and best friend, thank you for always standing by me, supporting me and believing in me.

To my mom and dad, thank you for always pushing me to be better and teaching me to follow my dreams.

To my wonderful and brilliant sister, thank you for listening, advising and supporting me through it all.

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LIST OF ABBREVIATIONS

- CINV- Chemotherapy induced nausea and vomiting
- LHSC- London Health Sciences Centre
- LRCP- London Regional Cancer Centre Pharmacy
- PRN- As Needed
- RCT- Randomized controlled trial
- REB- Research Ethics Board

INTRODUCTION

GENERAL INTRODUCTION

Adherence, for the purpose of this thesis is defined as the degree to which a patient's medication behaviours correlate with the therapeutic recommendations agreed upon with their treating care provider, and is an essential component of drug therapy(Font et al., 2017).

A Cochrane review focusing on interventions that affect "adherence", quantify adherence as the number of doses taken of a prescribed agent divided by the number of doses prescribed (Haynes et al., 2005). A calculation of adherence, which will be used as a basis of hypothesis generation and for the purpose of calculating a numerical adherence for this document, can also be found in the figure below (Figure 1).

FIGURE 1: CALCULATING SELF-REPORT ADHERENCE

Self-report adherence

$$\% \text{ adherence} = \frac{(\text{number of tablets taken per day as reported by client})}{(\text{prescribed number of tablets per day as on label})} \times 100$$

FIGURE 1

Adherence has also had historical difference when gender was taken into consideration with one study indicating that women were less likely than men to be adherent to chronic medications prescribed (Manteuffel et al., 2014). Furthermore, another study that assessed factors which affect gender difference in medication adherence that focus on management of hypertension also re-asserts the fact that male

participants adherence more effectively than female participants do (Chen, Lee, Liang, & Liao, 2014). Therefore, it must be taken into deliberation that depending on the gender of a particular population, especially when a disease is predominate to one gender over another, such as breast cancer being more frequent in females and prostate cancer found solely in males, demographic factors must be noted.

Although adherence in the traditional sense focuses on how well patients comply with a prescribed medication regimen, adherence also must take into consideration the symptoms that participants are experiencing on medications, tolerability of medications, pill burden and other external factors, such as cultural beliefs and socioeconomic factors.

According to data from the World Health Organziation and a study by Brown & Bussell, adherence to long-term therapy for chronic illnesses in developed countries averages approximately 50% (Sabate, n.d.), (Brown & Bussell, 2011). In consequence, non-adherence may lead to reduced efficacy and increased healthcare costs.

These approximate estimates are at times an over-estimation due to self-reporting of data. A review on medication adherence by Matsui in 2013 states that the more complex and convoluted a medication regimen is, the less likely that it will be followed (Matsui, 2013). The author also states that poor medication adherence is common and at times prevalent in multiple disease conditions where the lack of adherence can potentiate failure of therapeutic goals and lead to worsening illnesses (Matsui, 2013).

There are a multitude of reasons why non-adherence occurs, which includes factors such as poor communication between the health care professional and the patient, a cognitive inability to understand instructions given, possible intentional non-adherence

(Morrow, Leirer, & Sheikh, 1988) and other sometimes, patient specific reasons. Therefore, tools, education and other modalities must be synergistically applied in order to improve patient adherence to medication regimens.

Poor adherence to drug therapy can take multiple forms including, but not limited to not having prescriptions filled for a disease state, and not strictly following or discontinuing medication regimens without consultation with a health care professional (Matsui, 2013). Patient non-adherence can also be related to unpleasant side effects of the medication, lack of education on medication administration, or convoluted medication regimens (Claxton, Cramer, & Pierce, 2001; Kreps & Sparks, 2008; Shrank & Avorn, 2007).

Aside from adherence being due to changes in the use of a prescribed medication by a knowing participant, it may also be due to reduced health literacy. In the United States, approximately half of patients have poor health literacy (Shrank & Avorn, 2007), which can propagate confusion and an inability to adhere to medication regimens, even if the intent is to do so.

A study by Kreps and Sparks has shown that patients with low health literacy often have difficulty comprehending medical instructions; amongst this group, pictorial aids have been found to be helpful (Kreps & Sparks, 2008). Although the majority of the literature focuses on visual aids being effective in the lower health literacy population, patients often use pictures and words in information monographs to guide their medication taking behaviours.

ADHERENCE IN THE ONCOLOGY POPULATION

In recent years there has been significant progress in treatment of oncologic processes, which has been accompanied by increased regimen complexity. Patients must not only grasp the regimens and side effects associated with chemotherapy and indications of supportive care medications in the oncology setting but must also remember when certain medications are to be taken. Due to the increasing complexity and at times overwhelming nature of disease treatment, there is a significant focus on maintaining and improving quality of life of individuals living with cancer and their caregivers (Canadian Cancer Society's Advisory Committee on Cancer Statistics., 2016). Adherence to oncologic regimens, as well as the supportive care regimens accompanying chemotherapeutic and biologic treatments, is an essential component of managing the oncologic process and ensuring that the quality of life of patients is as optimal as possible.

A study by Font et al. notes that adherence to neo-adjuvant treatment utilizing capecitabine varied from 100% on clinical history, 83% on self-report and 67.9 % on pill count (Font et al., 2017). This data is cause for alarm as studies that exist in the literature to assess efficacy, disease free progression and cure rates generally require exceptional follow-up and adherence. Furthermore, the authors note that self-reported adherence has historically tended to over-estimate true adherence (Font et al., 2017). Therefore, when utilizing tools, such as diaries, which require a subjective recording of the participant's medication use behaviour, the investigator must be aware that the values attained may over-estimate true use.

In another study that assessed medication adherence to oral cancer therapies, adherence ranged from 20 to 100% (Felton, van Londen, & Marcum, 2016), which is a wide and concerning range. This wide range of adherence to oral cancer therapies creates a difficulty in deciding what is the goal, or expected adherence to these medications in the real world.

In a report that compared non-adherence with adjuvant anastrozole therapy using three separate databases in the same population, estimates of non-adherence varied from 32-50% (Patridge, AH, LaFountain, A, Mayer, E, Taylor, BS, Winer, E, Asnis-Alibozek, 2008). Another study regarding adherence in tamoxifen users ranged from 41-88%, whereas adherence in aromatase inhibitor users ranged from 50-91% (Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012).

Outside of adherence to the chemotherapeutic agents, compliance with supportive medication use, such as agents used to manage nausea and vomiting area also important. CINV is a significant and distressing problem for patients receiving moderate or highly emetogenic chemotherapy (Gilmore et al., 2014). Multiple supportive care medications have been used to manage or prevent CINV (Gilmore et al., 2014), however, patients must be educated and sometimes reminded on the appropriate use of these supportive care medications due to the complexity of the regimens.

Adherence to chronic medication use, such as tamoxifen regimens which persist for 5 years or more and that associated with short courses of anti-emetics used around neo-adjuvant or adjuvant chemotherapy, is quite different and may not be extrapolatable to short bursts of drug therapy. A patient receiving an anti-emetic regimen has to comply

to multiple and different pills taken per day for on a general basis 3 to 5 days, however a patient taking tamoxifen uses the same dose every day for many years. Whether adherence would be better in one group versus the other is not clear.

FURTHER COMPLEXITIES OF ADHERENCE

Aside from the complexity and side effects associated with oncological regimens, many cancers affect Canadians aged 50 years and older more than other age groups (Canadian Cancer Society's Advisory Committee on Cancer Statistics., 2016). This population may be at higher risk of concomitant illnesses such as diabetes, hypertension (Yancik, R., 1997) as well as memory decline and, thus, require a multitude of other medications for the management of these chronic illnesses. The pill burden associated with chronic disease state management as well as supportive-care medication management for oncological regimens creates a more complex picture, which can increase non-adherence. Furthermore, confusion secondary to the disease states themselves, such as cognitive decline, sedation secondary to anticholinergic agents or other drug-induced adverse effects reduce the patient's ability to comply with and remember medication instructions.

Elderly patients may have difficulty reading and understanding drug labels such that only 40% of older patients in a particular study clearly understood how to properly take medications (Shrank & Avorn, 2007). It must be taken into consideration that the much older adult population would be more likely to suffer from visual and hearing impairment and have difficultly understanding instructions due to reasons other than poor compliance or medication taking behaviours.

A post-hoc analysis was performed by the Kripalani et al., which found that medication schedules led to significantly greater odds of adherence for those who had more than eight medications at baseline (OR=2.2; 95 % CI, 1.21 to 4.04) (Kripalani, Schmotzer, & Jacobson, 2012).

A study by Ngoh L and Sheperd M., on the use of visual aids for communicating prescription drug instructions to non-literate patients found that culturally sensitive visual aids presented in a pictorial format significantly improved comprehension and compliance to the antibiotic agents prescribed (Ngoh & Shepherd, 1997). The authors stipulated from previous literature that there are key aspects, which make visual aids effective. The first is that the visual aid must get the participant's attention and must be representative of the object it is to emulate (Ngoh & Shepherd, 1997). Secondly, visual representations must be culturally sensitive (Ngoh & Shepherd, 1997). Lastly, the clinician must take into consideration that the tool is generally developed by a professional and is often unable to capture the cultural references that must be applied to be understood (Ngoh & Shepherd, 1997). Therefore, multiple considerations must be noted when creating adherence based regimens and tools to improve medication taking behaviours of patients.

Shrank et al. elude to the fact that information labels and inserts are generally significant sources of information for patients when determining the benefits and risk of adverse effects associated with medication administration, however the quality of this information often varies significantly (Shrank & Avorn, 2007). Therefore, standardization of education and information tools aimed at improving medication taking

behaviours and ensuring that tools take into consideration patient key beliefs and values would create more effective tools.

ADHERENCE TOOLS IN THE LITERATURE

Adherence is a multifactorial concept that depends on a chain of communication that encompasses many stakeholders from physician, to pharmacist, nursing staff and the patient (Morrow et al., 1988). The process of medication taking is not simple and has many areas where errors are possible. First, the physician must write a prescription for a medication, then the patient must take the prescription to be filled at a pharmacy (Morrow et al., 1988). The pharmacist must then dispense the correct medication and guide the patient on appropriate therapy, which often does not take into consideration the pill burden of multiple medications (Morrow et al., 1988). Even with modern day technology where prescriptions can be written on a computerized interface and sent to a pharmacy directly, the same process applies where a prescription must pass between prescriber, pharmacist and patient.

The patient must then remember to take the correct dose at the right time and remember all drug and food interactions that were discussed with the prescriber and pharmacist (Morrow et al., 1988). All of these factors are often complicated without any external factors, however when cognitive impairment or another adherence impeding factor is brought into the equation, adherence becomes much more difficult. Therefore, tools to reduce the complexity of the regimen or to act as a reminder to patients are possible methods to improve adherence.

According to Kreps et al., health communication and education messages must be strategically designed to meet unique needs and communication orientations of target audiences (Kreps & Sparks, 2008). Messages should be designed to meet key beliefs, attitudes and values of the target population and ensure that messages, language, and illustrations are appropriate (Kreps & Sparks, 2008). Adherence interventions, including educational material and programs as well as written instructions and calendars are helpful but often-labor intensive and not feasible in a clinical setting (Morrow et al., 1988). However, if an intervention can be simplified in order to reduce clinician workload, the intervention may be not only effective, but also feasible.

There are multiple medication adherence strategies that exist in the literature, including medication vial caps that remind patients to take medications and phone application reminders (Felton et al., 2016). However, according to a review of the literature on the use of pictorial aids in medication instructions, humans tend to have a cognitive preference for pictures (Katz MG, 2006). Also, a combination of text and pictorial instruction appears to be more effective than either format alone to improve adherence to medications (Katz MG, 2006). Katz, the author of a review article on visual aids and medication adherence alludes to the need for pictorial depictions to be realistic, simple and have a clear singular meaning in order to be effective (Katz MG, 2006). Scientifically, there appears to be evidence suugesting that pictures aid in the development of a cognitive model that improves problem solving (Katz MG, 2006).

Katz conducted a MEDLINE search of app data published between 1966 to 2005 using terminologies such as “illustration, picture, pictograph, graphics, chart, image, photo, cartoon and drawings”(Katz MG, 2006). The authors also assessed search terms

which included “pill, medicine, pharmacy, prescription, etc.” (Katz MG, 2006). The following were key messages present in this review regarding increasing effectiveness of health communication that were focused upon when gathering information for the purpose of this thesis and was considered during the formulation of the research question for this RCT (Kreps & Sparks, 2008). First, individuals from the population of interest should be involved and empowered when creating a health communication method (Kreps & Sparks, 2008). Secondly, culturally appropriate messages and materials should be created (Kreps & Sparks, 2008). Thirdly, a focus should be placed on care providers and community members to deliver and reinforce messages (Kreps & Sparks, 2008).

ADHERENCE METHODOLOGY IN THE LITERATURE

A study by Dowse and Ehlers was conducted in 87 participants who attended an outpatient clinic and were prescribed a short course antibiotic (Dowse & Ehlers, 2005). The authors utilized previously developed and tested pictograms that were culturally sensitive and were printed on the reverse side of a re-sealable plastic packet routinely used in the region (Dowse & Ehlers, 2005). Participants received followed up 3 to 5 days after antibiotic initiation to test recall and understanding of the medication instructions (Dowse & Ehlers, 2005). Adherence was determined using self-reporting and pill or medication count (Dowse & Ehlers, 2005). The statistical analysis performed by study authors was a chi-squared test to assess for significant differences in demographic characteristics between the control and intervention group and to test for differences in understanding of medication instructions and adherence (Dowse & Ehlers, 2005). The influence of literacy on both understanding and adherence was investigated using a

correlation analysis and the level of significance was set at 1% (Dowse & Ehlers, 2005). According to the authors, the use of a pictogram enhanced patient comprehension (Dowse & Ehlers, 2005).

Another study focused on simulated labels and compared the design of the labels to determine if text only, pictures only or text and words would affect patient understanding of medication instructions (Sansgiry, Cady, & Adamcik, 1997). The authors found that the method of label design significantly affected participant understanding of the medication instructions. The authors did not, however, find a significant difference between individuals that received text and picture versus text alone (Sansgiry et al., 1997).

Another study was performed with low health literacy participants with difficulty understanding medication instructions at baseline (Kripalani et al., 2007). Participants in the intervention group received a card with medication name, indication and time of administration (Kripalani et al., 2007). The pill card was reported frequently use by the intervention group initially, however its use declined approximately 3 months later (Kripalani et al., 2007). Participants with lower health literacy utilized the pill cards regularly and found it helpful for remembering important medication information (Kripalani et al., 2007). Therefore, this tool was helpful for participants with lower health literacy according to the study results.

Our hypothesized definition of adherence revolved around adherence to the prescribed supportive care regimen for nausea and vomiting 80% of the time for scheduled medications. The selection of 80% adherence rate is relatively arbitrary as the

actual adherence in the literature varied significantly. The assumed average adherence rate for the general oncology population that entered the study for treatment of adjuvant and neoadjuvant malignancies without the use of an adherence calendar was assumed to be an average of 60% according to the above-mentioned statistics (Sample Size).

PHARMACIST'S ROLE IN PATIENT'S MEDICATION TAKING BEHAVIOURS

A study on the role of the pharmacist in medication adherence in the oncology setting supports the pharmacist's role is multifactorial team environments, in that the pharmacist includes written and oral communication to the patient, counselling and follow-up over time as appropriate (Felton et al., 2016).

A recent randomized controlled study conducted by the Ontario Pharmacists Association and Green Shield of Canada addressed the impact of pharmacist interventions in hypertension management on patient outcomes and discussed a few key strategies used to improve adherence ((OPA) & (GSC), 2014). The strategies involved a multi-modal approach that included: simplifying regimen characteristics, ensuring that patients understood the purpose of the medication, addressing the risks of non-adherence and benefits of treatment, communicating in a manner that is understandable to the patient and evaluating adherence ((OPA) & (GSC), 2014). This pharmacy led approach allowed for a quadrupling in the number of patients whose blood pressure was controlled and increased medication adherence by 15% ((OPA) & (GSC), 2014).

Furthermore, according to multiple surveys summarized by Felton et al., patients in an ambulatory outpatient oncology clinic indicated that it was "absolutely necessary"

to discuss initial treatment with a pharmacist 86% of the time (Felton et al., 2016). Also in the same commentary article, 76% of participants requested that discussion with a pharmacist occur at follow-up visits (Felton et al., 2016). Therefore, it is clear that the involvement of a pharmacist is invaluable to patients and the inclusion of a pictorial medication calendar to help guide discussion may result in better medication taking behaviour and understanding by the patient.

Therefore, the above-mentioned examples allude to the necessity of a multidisciplinary and multi-modal strategy to improve adherence. This information is not specific to either hypertension or oncology and can be applicable to all adherence strategies. A major role of the pharmacist is to allow for patients to understand more thoroughly the purpose of the medications, how to use them and expected adverse effects associated with chemotherapeutic and supportive care medications prescribed.

PURPOSE OF STUDY

Secondary to the complexity of oncologic supportive care regimens, particularly in moderately or highly ematogenic and myelosuppressive chemotherapies, the author wished to examine if the use of a visual aid would improve patient adherence. A preliminary qualitative survey conducted by nursing staff and pharmacists in 2010-2011 at the London Regional Cancer Program at London Health Sciences centre in London, Ontario using the pictorial medication calendar tool proposed in this study, generated very positive results regarding participant satisfaction with the pictorial medication calendar (Smith, 2012). The survey found over 80% of 38 patients moderately or completely agreed that the calendar helped them to better understand medications (Smith,

2012). Similar results were obtained from the healthcare staff, which saw this tool as a tremendous aid to patients (Smith, 2012). Over 95% of 29 staff agreed that the calendar helped their patients better understand what medications they needed to take and when to take them (Smith, 2012). The survey was intended to assess the usefulness of the tool from a health care provider and patient point of view and not to determine if the tool was effective in improving adherence or medication taking behaviours objectively.

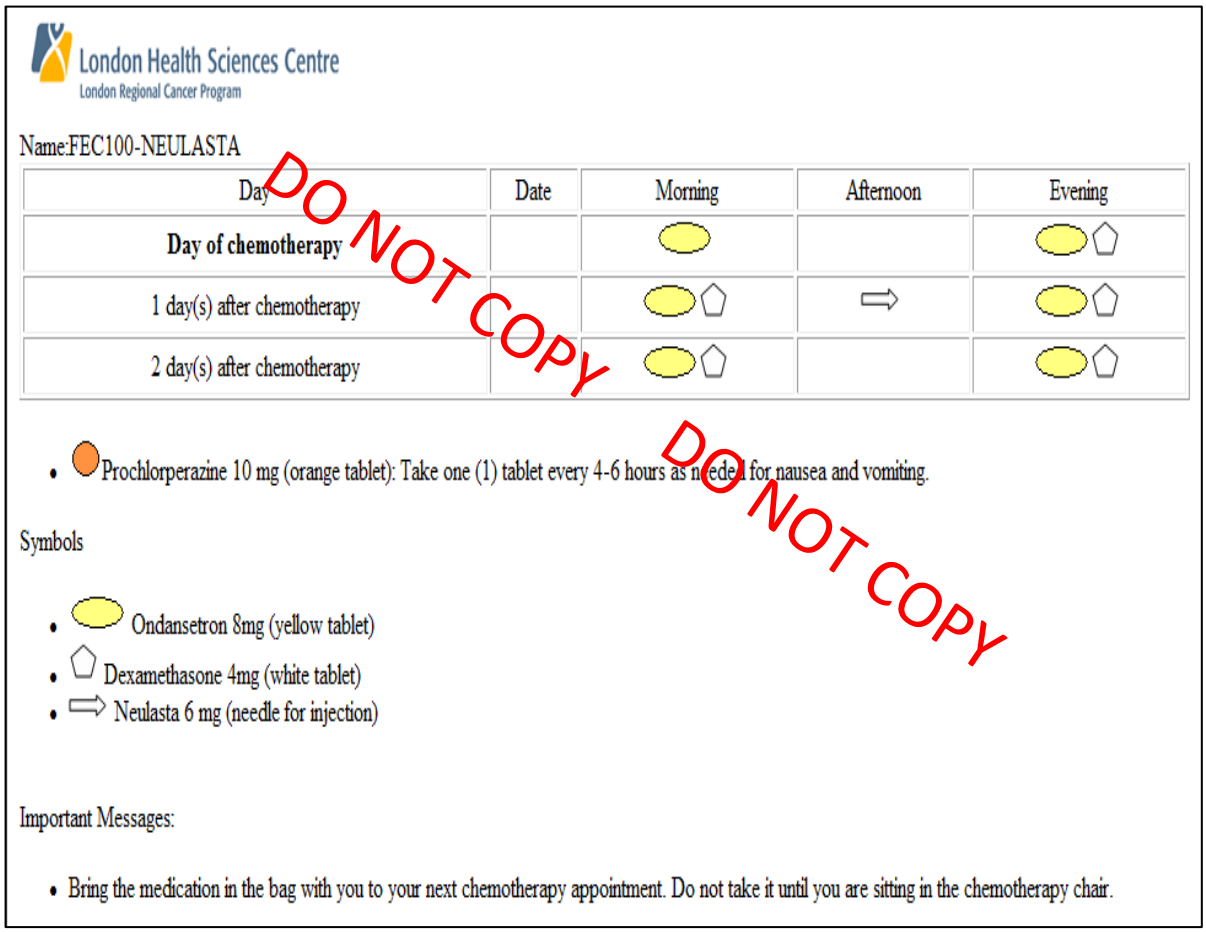
Therefore, an RCT was created to determine if this particular visual aid, a pictorial medication calendar created by an oncology pharmacist at the LRCP would improve adherence to supportive care medications and affect other medication taking behaviours of patients.

The pictorial medication calendar is an amalgamation of pictures of the respective medications and instructions on how to take the medications (Figure 2). A figure in the supplemental literature of this thesis provides an example of these pictorial medication calendars ((Figure 2). The calendars are created by LRCP pharmacists and can be saved and modified by the pharmacy team. The calendars are then printed in colour to allow for patients to have not only instructions on the vials to guide their medication taking behaviours but also another learning tool, which activates different parts of the brain to ensure learning and understanding are multifactorial (Katz MG, 2006).

We proposed that use of this pictorial medication calendar tool would improve patient adherence and understanding of how to take medications through simplification of presentation and the addition of pictographic information. This tool allows the patient to see the medication regimen in a visual format. The calendar can also be divided into the

various times of day that medications should be taken, followed by the corresponding symbols for each medication on the calendar, which allows patients to know which pill to take and when. This tool also has the potential to add in messages and comments about the medication at the bottom of the calendar (Figure 2).

FIGURE 2: FEC-100 "CALENDAR" REGIMEN EXAMPLE



London Health Sciences Centre
London Regional Cancer Program

Name:FEC100-NEULASTA

Day	Date	Morning	Afternoon	Evening
Day of chemotherapy				
1 day(s) after chemotherapy				
2 day(s) after chemotherapy				

- Prochlorperazine 10 mg (orange tablet): Take one (1) tablet every 4-6 hours as needed for nausea and vomiting.

Symbols

- Ondansetron 8mg (yellow tablet)
- Dexamethasone 4mg (white tablet)
- Neulasta 6 mg (needle for injection)

Important Messages:

- Bring the medication in the bag with you to your next chemotherapy appointment. Do not take it until you are sitting in the chemotherapy chair.

FIGURE 2

OBJECTIVES

Our primary objective is to examine if this visual aid, the oncology pictorial medication calendar, improves patient adherence to oncology supportive care medication regimens for adult patients receiving treatment for adjuvant or neoadjuvant solid organ cancers using an open-label, randomized controlled study.

Our secondary objectives are to assess whether the use of this medication calendar will improve concordance with prescribed PRN supportive care medication regimens, medication use and self efficacy with a focus on nausea and vomiting management, and patient satisfaction, and whether this tool helps to alleviate workload hours for pharmacy and nursing staff.

HYPOTHESES

ADHERENCE

The null hypothesis would argue that the use of a pictorial medication calendar does not affect adherence to scheduled anti-emetic regimens used alongside chemotherapy in the neo-adjuvant or adjuvant oncology population receiving treatment for a non-hematologic malignancy. The alternate hypothesis would argue that the use of a pictorial medication calendar does affect adherence, with those in the intervention group being able to take scheduled medications more effectively than those in the control group.

MEDICATION USE AND SELF-EFFICACY (MUSE)

The null hypothesis for MUSE scale results would state there would not be a statistically significant difference between the participant scores at baseline to end of study. The alternative hypothesis for the MUSE scale results would state that there is a statistically significant difference between the participant scores at baseline to end of study.

SYMPTOM MANAGEMENT

The null hypothesis is that the use of the pictorial medication calendar would not improve concordance between, PRN antiemetic use and symptom management of nausea and/or vomiting. The alternative hypothesis would be that the use of the pictorial medication calendar improves concordance between, PRN antiemetic use and symptom management.

The null hypothesis would state that participant satisfaction with the complexity of the anti-emetic regimen would not be affected by the use of pictorial medication calendar. Furthermore, the null hypothesis would also argue that participants receiving the intervention would not be more satisfied than the neutral response with medication use behaviour outcomes. The alternative hypothesis would argue that the use of the pictorial medication calendar is associated with higher satisfaction in the intervention population with the anti-emetic regimen's complexity. Also, those who receive the intervention would completely agree with the usefulness of the tool for medication taking behaviour improvements.

METHODOLOGY

EXPERIMENTAL DESIGN

A prospective, open-label, randomized controlled study was conducted in the outpatient oncology setting. Participants were randomly assigned in a 1:1 manner to receive routine care versus routine care plus the medication calendar. Routine care consisted of an oncology pharmacist counselling the patient prior to the patient receiving their medications. The intervention group involved the oncology pharmacist using the computer system to print a medication calendar for the patient and explaining the calendar, in addition to routine care.

Pharmacists were trained and provided a script to ensure that similar teaching was given to each participant is used in the two groups to reduce the risk of bias. Wording of the scripts for pharmacist counselling was as follows:

For scheduled anti-emetics:

This medication is used to help control your symptoms of nausea and/or vomiting. This medication is to be taken _____ (regimen).

For PRN anti-emetics:

This medication is used when needed to control symptoms of nausea and/or vomiting. This medication is to be taken _____ (regimen).

A pharmacy procedure sheet and process flow diagram was made available to all LRCP pharmacy staff members to ensure a systematic process was followed (Figure 3).

FIGURE 3: STUDY PROCESS

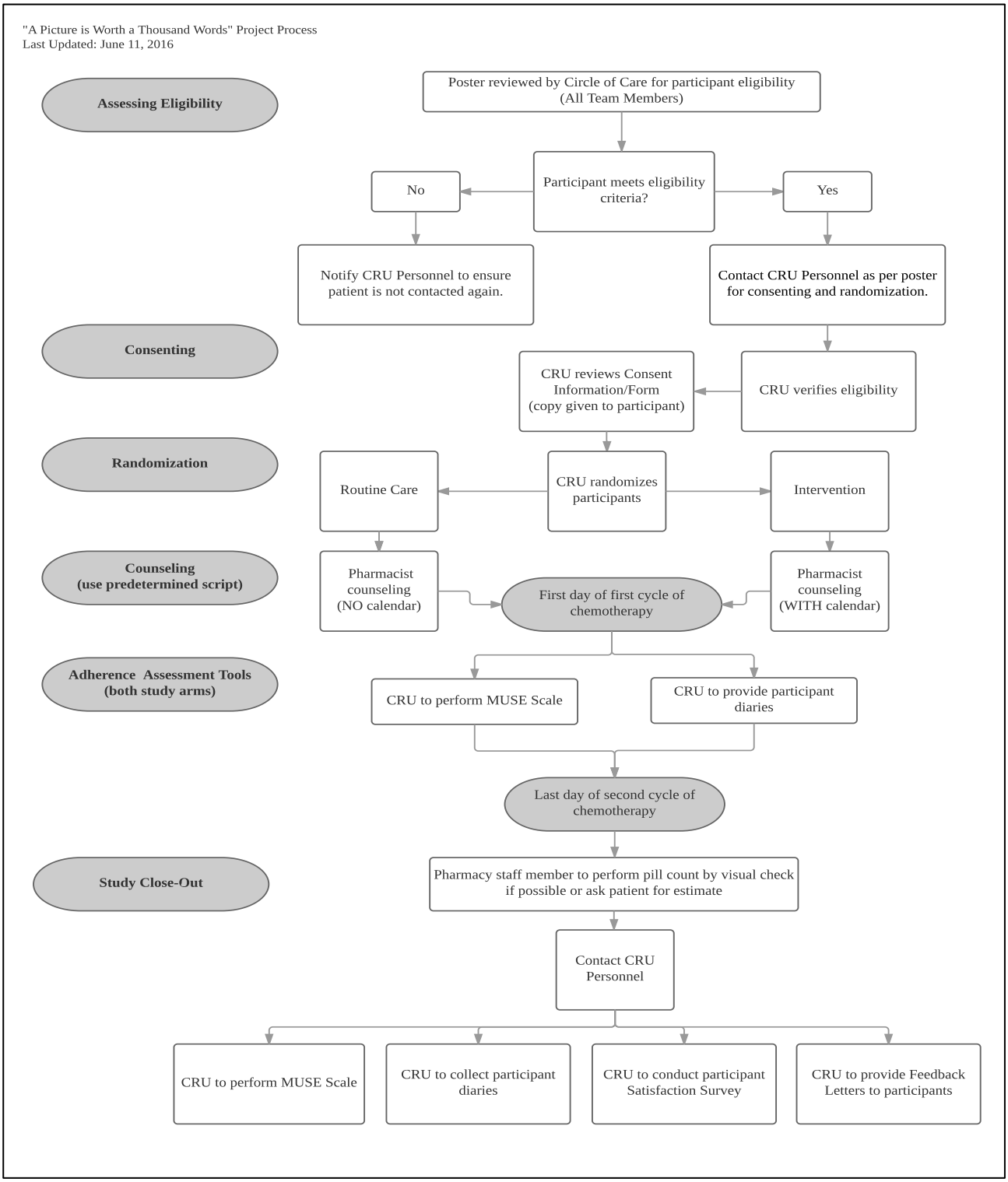


FIGURE 3

Patients were included in the study only for the first two cycles of chemotherapy treatment to reduce heterogeneity since patients may receive a different total number of cycles.

LOGISTICS

The study was conducted at the LRCP for the duration of 9 months and it is intended that a further extension will be requested to ensure that 174 participants are recruited if possible (see statistics component under the heading (Sample Size). LRCP has an annual patient flow of more than one million visits. As a part of LHSC, it is a well-established teaching, research and health-care facility. LRCP also has a team of oncology pharmacists and a clinical research unit. This pictorial medication adherence calendar was first developed and pilot tested at the LRCP. Preliminary studies conducted in 2011 at the LRCP included patients, nursing and pharmacy staff. Participants completed a survey to evaluate the pictorial medication calendar tool. The response rate for the patients was 75% (Smith, 2012). The results were very positive with over 80% of patients moderately or completely agreeing that the calendar helped them to better understand their medications and when to take them (Smith, 2012).

INCLUSION CRITERIA

Participants included adult male or female outpatients 18 years or older receiving chemotherapy treatment for neoadjuvant as well as adjuvant solid organ cancers. The primary populations enrolled included breast, colorectal and head & neck cancer.

Participants were on at least one scheduled antiemetic for management of chemotherapy-associated nausea and vomiting and were also given one PRN antiemetic.

Only participants able to provide consent for themselves were considered as this study assessed adherence of the individual patient to the medication regimen. In order to be able to provide consent, study participants must have been able to understand the instructions explained by the pharmacist for the adherence calendar and must have understood instructions provided by the Clinical Research Unit (CRU) consenting staff. Participants with speech or hearing impairment were given the opportunity to communicate in writing with the investigators.

EXCLUSION CRITERIA

Participants who had not attained a minimum of a grade 8 education as well as non-English speaking individuals were excluded since fluency with the English language was necessary to interpret the medication calendar. Currently the calendar is only available in the English Language.

If the participant was unable to repeat the instructions back to research personnel at baseline, or becomes increasingly confused as time progressed, or a care provider had to speak on the participant's behalf, the participant was withdrawn from the study. Participants were also withdrawn from the study if follow-up became difficult because participants were frequently rescheduled or missed.

Participants with difficulty swallowing and who required liquid formulations of medications were excluded from the study as the supportive care medication pictures

used for the calendars are created to take into consideration the pill format of medications. Participants who might eventually require liquid formulations of anti-emetics secondary to an oropharyngeal cancer or radiation therapy to the head or neck were included and re-assessed as required if swallowing difficulty developed.

Participants planning to receive multiple cycles of chemotherapy at baseline at sites other than the LRCP were generally excluded from the study if the plan was clear from the outset of chemotherapy treatment due to lack of ability to follow-up with pill counts and adherence diaries for these individuals.

Participants with a significant visual impairment that precluded the ability to read the pictorial medication calendar were excluded from the study.

ETHICS BOARD APPROVAL

The study personnel sought prior Research Ethics Board (REB) approval at Lawson Research Institute in London, Ontario and the University of Waterloo Ethics Board for the full study.

Supporting documentation that were submitted and approved by the Ethics Boards, included:

- Consent Form and Information (Appendix A: Information and Consent Form),
- Feedback Letter (Appendix B: Feedback Letter),
- Study Poster (Appendix C: Study Poster),
- Accountability Log (Appendix D: Accountability Log),
- Adherence Diary (Appendix E: Adherence Diary),

- Study Survey (Appendix F: Study Survey)
- Randomization and Enrollment Form (Appendix G: Randomization and Enrollment Form),
- Protocol Deviation Form (Appendix H: Protocol Deviation Form),
- Visit Checklist (Appendix K: Unanticipated Problems Form),
- Study Completion Form (Appendix J: Study Completion Form)
- Unanticipated Problems Form (Appendix K: Unanticipated Problems Form)

The study personnel intend on registering the study with clinicaltrials.gov.

STUDY PROCEDURE

The study investigators obtained consent from all attending physicians to approach patients for the study prior to enrollement of participants from each disease site. Physicians and CRU staff received a notification of an eligible participant. CRU personnel verified that the LRCP patient screened by a health care provider met the inclusion and exclusion criteria. CRU personnel discussed the study with the eligible patient and provided the patient with an informed consent form, if not already provided by the circle of care team member, to be completed up until the first day of the first cycle of chemotherapy. The study procedure flow diagram provides further information regarding the process of approaching eligible participants (Figure 3).

If consent was obtained, the CRU then randomized the participant according to the randomization algorithm provided by the research personnel and notified the pharmacy team of the patient's randomization status (Figure 3). The pharmacist then

provided routine care, consisting of counselling the patient prior to the patient getting his or her prescription dispensed if randomized to the routine care arm. The pharmacist provided routine care and explained the medication calendar for the patient randomized to the intervention arm. Pharmacists were given a script that indicated general wording to be used when counselling participants in both the control and intervention groups. Pharmacy staff ensured that the accountability log (Appendix D: Accountability Log) was filled out for pill counts, counselling and notes where applicable.

Before the patient left the LRCP on the first day of the first cycle of chemotherapy, CRU personnel provided the patient with a diary (Appendix E: Adherence Diary) to log information on the supportive care medication taken for nausea and vomiting, date, time, number of pills, and subjective assessment on a scale of 1 to 10 of the symptoms felt that day. Instructions for completion of the diary were on the first page. At the end of the first 2 cycles of chemotherapy, the CRU provided a survey to all study patients (Appendix F: Study Survey), which asked questions regarding satisfaction with their regimen's complexity, satisfaction with the calendar for the intervention arm and demographic information.

DATA RETENTION

A Master Log was maintained in a locked filing cabinet at the study centre. Data was de-identified by ensuring each participant receives an alphanumeric code. A de-identified data collection log was retained for study analysis purposes at the study centre.

The hardcopy master list and consenting information sheets will be erased or placed in the confidential shredding bins 1 year from the date of completion of data

collection for this project as per Ethics Boards guidelines. Primary data documents (such as the diary, surveys and questionnaires) that were de-identified are stored at the study site for 5 years and will then be placed in the confidential shredding bins.

Data that was de-identified and transferred to an electronic format via REDCap for analysis will be retained for 5 years and then erased. De-identified data that is shared between sites for analysis will be stored on an encrypted USB stick.

RANDOMIZATION PROCESS

A random sequence generated from "Random.org" was used to place participants in the intervention versus control arm (Dr. Haahr & Dr Haahr, 2017). The randomized sequence was used to create randomized manila envelopes numbered from 1 to 174 in sequence. A single co-investigator retained randomization sequence to ensure maintenance of study integrity only.

ANONYMITY

Collected information that was not in print format and at the study site was stored on the study site's private network on an encrypted server. Hardcopy data was de-identified at initiation and entered into an electronic database, REDCap (Harris et al., 2009). The hardcopy sheets that contained patient information with identifiers were stored only at the study site in a locked cabinet with study staff.

A site computer was always used when entering and storing data that had identifiable variables. If data sharing was required (e.g., when analyzing data), only de-

identified data was shared using an encrypted memory stick or a secure e-mail transfer. Access to the patient records and location of information storage was limited to authorized personnel on the research team. REDCap (Harris et al., 2009), a secure web application for managing and storing the online surveys and databases was accessible to study personnel only.

SAMPLE SIZE

Based on previous research, (Patridge, AH, LaFountain, A, Mayer, E, Taylor, BS, Winer, E, Asnis-Alibozek, 2008), (Murphy, Bartholomew, Carpentier, Bluethman, & Vernon, 2012), (Katz MG, 2006) we estimated a 20-30% difference in adherence to medication between groups. Sample size was calculated to determine the range of patients required to compare two independent proportions with 80% power, a 5% significance level (2-sided), and a 10% attrition rate (Rosner, 2011):

20% difference in proportion requires 87 patients per group

30% difference in proportion requires 40 patients per group

Thus, we estimated that data would be needed from between 40-87 patients in both groups to find a significant effect of adherence to medication. This results in a total estimated sample size of between 80-174 patients (Rosner, 2011); therefore, the upper bound of this interval was selected as the sample size.

To correlate the sample sizes utilized for similar primary outcomes in the literature, previous studies were also assessed with similar study methodology. A study by Dowse and Ehlers assessing adherence using either text-only or text plus pictogram

required n=87 ((Dowse & Ehlers, 2005). Another study by Mansoor and Dowse designed to evaluate understandability of labels and patient information sheets with or without incorporation of a pictogram had a sample size of n=60 (Mansoor & Dowse, 2003). Although methodology was similar, statistical significance of difference in adherence related to pill count was not the primary outcome of either study.

STATISTICAL ANALYSES AND DATABASES

Microsoft Excel and STATA (StataCorp., 2015) were used to interpret the data that was attained from input into the REDCap database (Harris et al., 2009). Study data were collected and managed using REDCap electronic data capture tools hosted at the Lawson Research Institute (Harris et al., 2009).

"REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources" (Harris et al., 2009).

MEASURES OF ADHERENCE

Adherence was defined as how well one takes a medication in relation to its prescribed dosing regimen (dose, interval and duration) (Zedler, Kakad, Colilla, Murrelle, & Shah, 11AD).

Adherence was measured in two distinct ways; using pill counts (Figure 1, Appendix D: Accountability Log) and a diary for patient self-tracking (Appendix E: Adherence Diary).

The pill counts were utilized to calculate the number of missed doses or pills taken as percentage of the total number prescribed and dispensed (Zedler et al., 11AD). Pill count took place during follow-up visits with the pharmacy team at the study site. Patients were asked at study initiation to bring their anti-emetics in for a pill count and all unused medications were returned to the patient.

A medication adherence diary (Appendix E: Adherence Diary) was also used to determine adherence from a patient's point of view and to assess symptom management for the nausea and vomiting. The adherence diary asked participants to keep track of the anti-emetic medications taken every day for the first two chemotherapy cycles.

The adherence rate between the pill count and diary entries was compared to determine inter-rater reliability (r). This was done to determine if the diary could be used as an independent and reliable tool for assessing adherence as the pill count was intended as a checking mechanism of adherence only rather than a measure in itself.

Adherence and concordance information were compared, where possible, between the control and intervention arms to determine if any of these parameters were affected by the introduction of a medication adherence calendar.

Adherence is a self-reported statistic and therefore pill count was compared to data reported in the diaries to determine agreement. A regression analysis was performed

on adherence data that was available from diaries to determine if there was a statistically significant difference in rates of adherence using pill count or in self-reported adherence.

CONCORDANCE

For medications to be taken PRN for nausea and vomiting symptoms, concordance was measured. Medications that are given on a flexible schedule, such as prochlorperazine 10mg every 4-6 hours PRN for nausea and vomiting, were measured in relation to the symptom being controlled.

A self-assessment of adherence was created that presumed a gradient of how many pills a patient would take based on their symptoms of nausea and vomiting since a validated algorithm was not available in the literature (Table 1).

TABLE 1: DETERMINING CONCORDANCE PERCENTAGES WITH PRN MEDICATIONS

Score of Nausea or Vomiting	Expected Percentage of Total Daily Doses Needed of PRN Medication	Percentage Expected to be Correlated with Number of Pills Taken* (i.e.. prochlorperazine 10mg take one tablet every 4-6 hours PRN for nausea and vomiting)
0	0	0
1-2	20%	1 tablet
3-5	40%	2 tablets
6-8	60%	4 tablets
9-10	80%	5 tablets
*** Rounding rules will be used to the nearest whole number**		

TABLE 1

The proposed ratios in (Table 1) were an assumption and may not reflect the true pattern with which participants use the PRN nausea and vomiting supportive care medications.

Concordance of the average nausea and vomiting symptoms over the two cycles with, PRN antiemetic use was calculated using a correlation and regression analysis.

MEDICATION USE AND SELF EFFICACY

Patient understanding was evaluated using the Medication Use and Self Efficacy (MUSE) (Cameron KA, Ross EL, Clayman ML, Bergeron AR, Federman AD, Bailey SC, Davis TC, 2010) scale. The MUSE scale is a self assessment tool that was modified and validated from an existing scale (Communication and Attitudinal Self-Efficacy Scale) (Cameron et al., 2010). The MUSE scale is a valid and reliable tool that is intended to measure self-efficacy and understanding of the use of prescribed medications (Cameron et al., 2010).

Participants were asked to complete the MUSE at the beginning and end of the study to determine if there was a change in the medication use and self-efficacy rating of participants between the beginning and end of their time n the study and also to determine if this was different between the two study arms. Correlation between scores was interpreted between baseline and study completion using a spearman's correlation statistic.

PATIENT SATISFACTION

Participant satisfaction was evaluated using the investigator created surveys (Appendix F: Study Survey). These surveys asked questions regarding complexity of the chemotherapeutic regimens, satisfaction with the pictorial medication calendar for the intervention arm as well as demographic information. Patient satisfaction surveys were completed at the end of the study. Patient satisfaction totals were tabulated for each question asked to determine overall subjective participant satisfaction with the pictorial medication calendar. Where applicable, a comparison between results in the intervention arm and control arm was planned.

OTHER DATA COLLECTED

Demographic information including gender, age and highest level of education attained were asked of participants in the study survey (Appendix F: Study Survey). This information was tabulated and presented in chart format by intervention group.

Information that may affect adherence related to supportive care regimen such as cycle length, number of times per day the that the participant takes non-oncologic medications and number of pills taken each time were collected to determine if the differences in regimens may contribute to differences in adherence (Appendix F: Study Survey).

RESULTS

DEMOGRAPHICS

33 participants have been enrolled thus far in the study; of those enrolled, 18 participants have completed the study. Of the participants who have completed the study to date, 1 did not complete the forms for end of study, including MUSE scale, satisfaction survey and return of diary. Of the 17 participants who have finished the study to date, 7 were randomized to the control arm and 10 were randomized to the intervention arm.

Of the 17 participants who completed the study, 35.29% (6 participants) were male and 64.71% (11 participants) were female (Table 2). 30% of the intervention group participants and 43% of control group participants were male (Table 2).

The average age in years of all participants was 59.17 with a SD of 2.91, with an age range of 37 to 78 years. The average age of participants in the intervention arm was 57 years and in the control arm the average age was 63 years (Table 2).

Of the 17 participants who completed the satisfaction survey, 2 participants attained a high school education, 6 participants attained a college education, 7 attained a university degree and 2 attained a post-graduate degree. The table found below provides a breakdown of education level by intervention arm (Table 2).

On average, participants in the intervention arm took 3.3 medications that are unrelated to their oncology regimen on a daily basis, including prescribed and non-prescribed medications and those in the control arm took 5.14 medications that are non-related to their oncology regimen (Table 2). The average number of times per day that

non-oncologic medications were taken equated to 1.5 versus 1.71 in the intervention versus control arm, respectively (Table 2).

TABLE 2: BASELINE DEMOGRAPHICS

Demographic Parameters	Control (n=7)	Intervention (n=10)
Average Age	62.71	56.70
Male Participant	3	3
Female Participant	4	7
Grade School Education	0	0
High School Education	1	1
College	2	4
University	3	4
Post Graduate	1	1
Average Number of Medications Unrelated to Oncology Regimen Taken per Day	5.14	3.3
Average Number of Times Per Day that Medication Unrelated to Oncology regimen is Taken	1.71	1.5

TABLE 2

CALCULATIONS OF ADHERENCE

Adherence was calculated using 2 different methods, pill count recorded in the accountability log (Appendix D: Accountability Log) and a subjective daily diary (Appendix G: Randomization and Enrollment Form) recording that was done daily. The number of prescribed scheduled medications was totaled for each cycle for both the data attained from the pill count and the diaries.

A correlation analysis was performed to determine the relationship between scheduled pills taken as per pill count performed by pharmacy and scheduled pills taken as per the adherence diary. The number of participants for which there was complete data for the diary was 11 out of 17, $r=0.60$ and $p=0.05$ (Table 3).

A correlation was also performed to determine how strongly associated the number of dispensed pills were to the number of pills taken as per the pill count and as per the diary. The expected correlation would be 1, assuming that participants took all scheduled anti-emetics prescribed to them. The correlation between scheduled pills dispensed and scheduled pills taken as per pill count was $r=0.96$ and $p<0.001$. The correlation between scheduled pills dispensed and scheduled pills taken as per the reported number in the diary was $r=0.71$ and $p=0.02$ (Table 3).

TABLE 3: CORRELATION BETWEEN SCHEDULED MEDICATIONS TAKEN AS PER PILL COUNT LOG AND DIARY

	Correlation of scheduled pills dispensed (# of participants)	Correlation of scheduled pills taken as per pill counts (# of participants)	Correlation of scheduled pills taken as per diary (# of participants)
Correlation of scheduled pills dispensed (# of participants)	r=1.00 (17)		
Correlation of scheduled pills taken as per pill counts (# of participants)	r=0.96 p=<0.001 (17)	r=1.00 (17)	
Correlation of scheduled pills taken as per diary (# of participants)	r=0.71 p=0.15 (11)	r=0.60 p=0.05 (11)	r=1.00 (11)

TABLE 3

A plot of the number of scheduled medications dispensed over the two cycles and the number of pills recorded in the patient's diary that were taken is provided in a scatterplot (Figure 4). Of the 10 participants in the intervention, 2 participants had a pill count performed at baseline by a pharmacy staff member, but did not bring the anti-emetic medications in for a pill count with each cycle (Figure 4). Of the 7 participants in the control arm, 4 participants were dispensed antiemetic medications for which the study personnel documented a pill count, however anti-emetic medications were not returned to pharmacy for a pill count (Figure 4).

FIGURE 4: PLOT OF NUMBER OF SCHEDULED PILLS DISPENSED AGAINST NUMBER OF PILLS TAKEN BY INTERVENTION ARM ON LEFT AND CONTROL ARM ON RIGHT

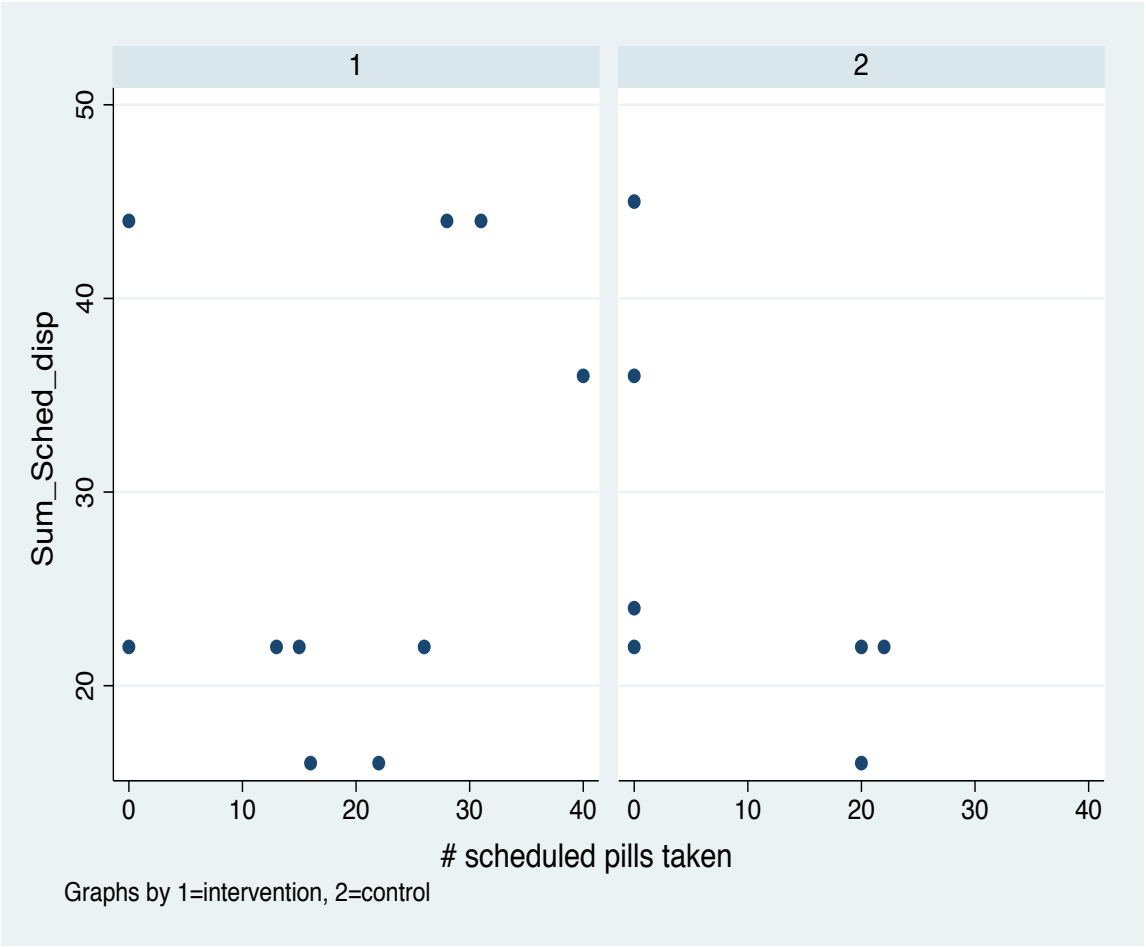


FIGURE 4

PRN ANTI-EMETIC USE AND CORRELATION WITH SYMPTOMS OF NAUSEA VOMITING SCORE AVERAGED OVER 2 CYCLES

A Spearman's correlation analysis was performed due to the non-normalized distribution of the data on the number of PRN pills taken and the average symptoms of CINV over the first two cycles and also to correlate the pill count and entries recorded in the diary for PRN medication use. 7 of the 17 participants did not return their diaries and therefore average symptom score of nausea and vomiting could not be calculated for those participants, the spearman's correlation was conducted by STATA on 9 study participants.

The Spearman's correlation coefficient between the number of PRN pills taken as per the pill count and average symptoms recorded in the diary was r=0.65 and p=0.06(Table 4). The Spearman's correlation coefficient between the number of PRN pills taken as per the diary and the average symptom score was r= 0.28 and p=0.47 (Table 4). The spearman's correlation coefficient between the PRN number of PRN pills taken as per the diary and the number as per the pill count was r=0.49 and p=0.19 (Table 4).

TABLE 4: SPEARMAN'S CORRELATION BETWEEN AS NEEDED MEDICATIONS TAKEN AS PER PILL COUNT LOG AND DIARY

	Correlation of PRN pills dispensed (# of participants)	Correlation of PRN pills taken as per pill counts (# of participants)	Correlation of PRN pills taken as per diary (# of participants)
Correlation of PRN pills dispensed (# of participants)	r=1.00 (9)		
Correlation of PRN pills taken as per pill counts (# of participants)	r=0.49 p=0.18 (9)	r=1.00 (9)	
Correlation of PRN pills taken as per diary (# of participants)	r=0.65 p=0.06 (9)	r=0.28 p=0.47 (9)	r=1.00 (9)

Table 4

A regression analysis was performed to determine if the symptoms of nausea and vomiting could predict PRN medication use (Table 5). There were 6 entries computable in the intervention arm and 3 in the control arm (Table 5). For the regression analysis model that assesses whether symptoms can predict PRN medication use in the intervention arm, $F(2,3)=7.24$, $r^2=0.83$, adjusted $r^2=0.71$, $p=0.04$, 95% CI[0.028, 0.41], line of best fit from the regression analysis would be y= 0.22 (pill count) - 0.01 (diary) + 0.61 (Table 5). Due to the low number of participant data in the control arm, a regression analysis was not possible.

TABLE 5: REGRESSION ANALYSIS OF PRN PILL COUNT AND DIARY RECORDING TO AVERAGE SYMPTOMS BY INTERVENTION ARM

Intervention Arm			Control Arm		
Number of observations=6 **F (2,3)= 7.24** **Prob >F= 0.07** **R-Squared= 0.83** **Adj R-Squared= 0.71** **Root MSE=1.39**			Not applicable, could not compute due to insufficient data **Number of observations=3**		
	Coefficient	**Std. Err**	**t**	**p> |t|**	**95% CI**
Intervention Arm (pill count)	0.22	0.06	3.66	0.04	0.03-0.41
Intervention Arm (diary)	-0.09	0.10	-0.09	0.93	-0.33-0.31
Control Arm (pill count)	0.77	-	-	-	-
Control Arm (diary)	1.31	-	-	-	-

TABLE 5

A graph of the number of PRN pills taken according to the diary entries plotted against the difference according to pill count can be found in the list of figures (Figure 5).

FIGURE 5: PLOT OF PRN MEDICATION CORRELATION

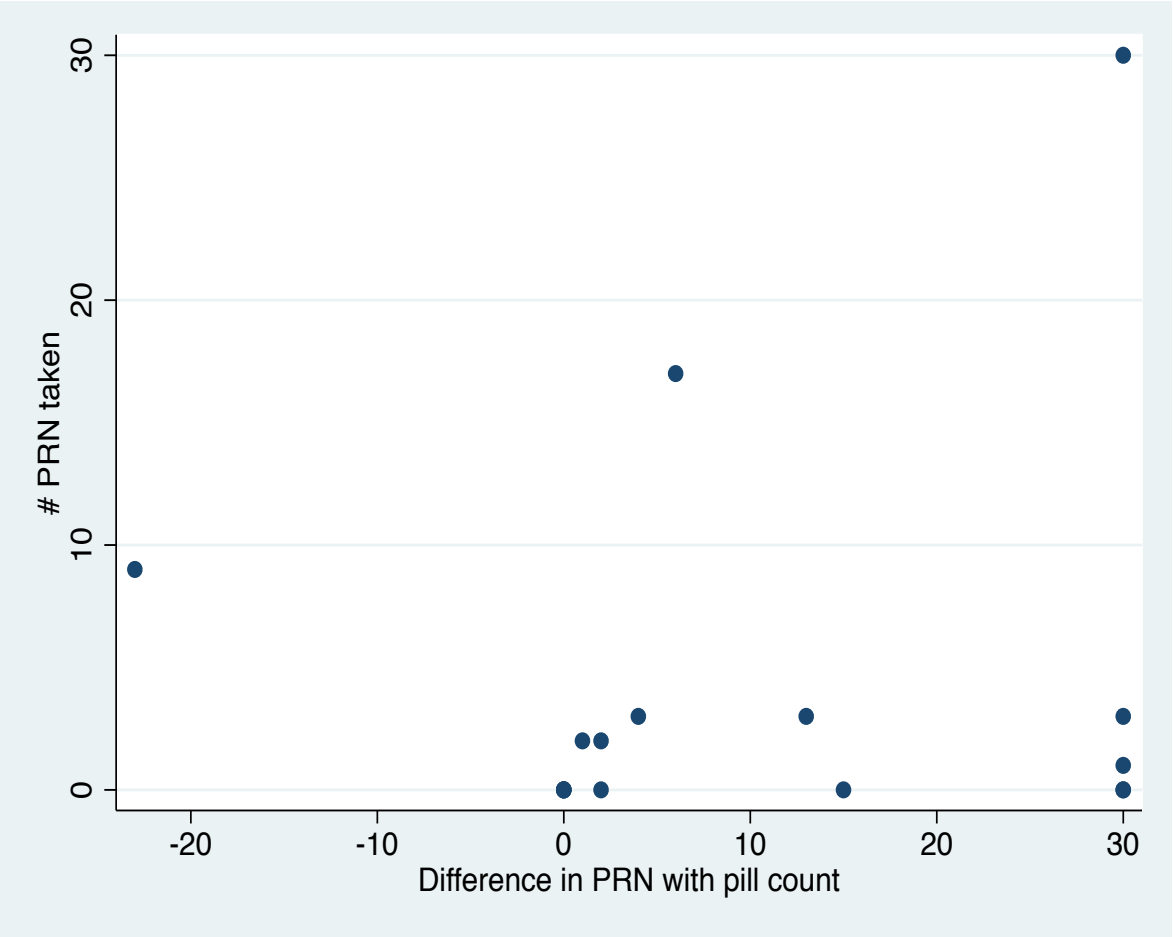


FIGURE 5

THE AVERAGE SYMPTOMS VERSUS PRN ANTI-EMETIC USE ACCORDING TO WHAT PARTICIPANTS RECORDED IN THE DIARIES WERE PLOTTED FOR THE INTERVENTION AND CONTROL ARMS. THE LINE OF BEST FIT FOR THE INTERVENTION ARM WAS Y= -0.09X + 3.06, R^2 = 0.05 (

Figure 6), and for the control arm, arm y= 1.11x + 0.16, R^2 = 0.92 (Figure 7).

FIGURE 6: AVERAGE SYMPTOMS VERSUS PRN ANTI-EMETIC USE (INTERVENTION)

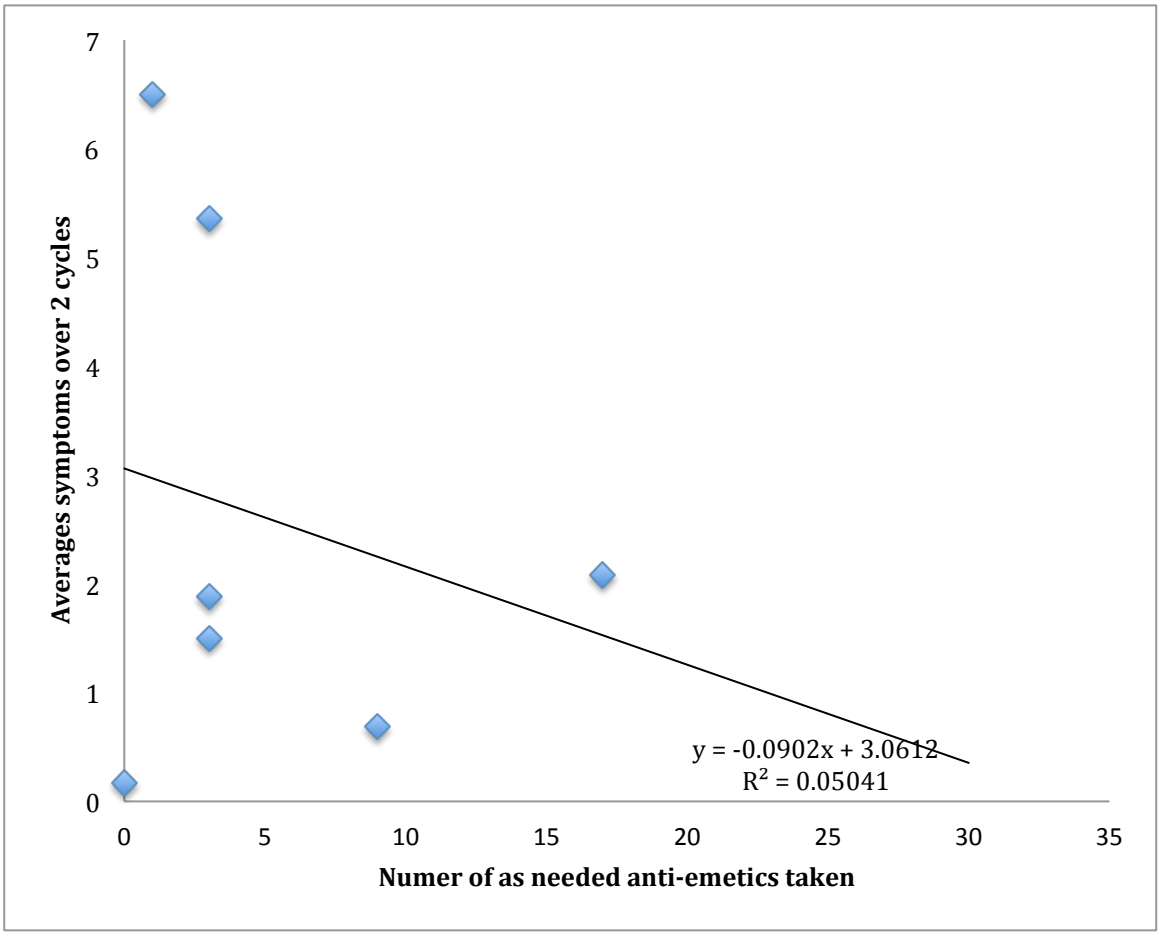


FIGURE 6

FIGURE 7: AVERAGE SYMPTOMS VERSUS PRN ANTI-EMETIC USE (CONTROL)

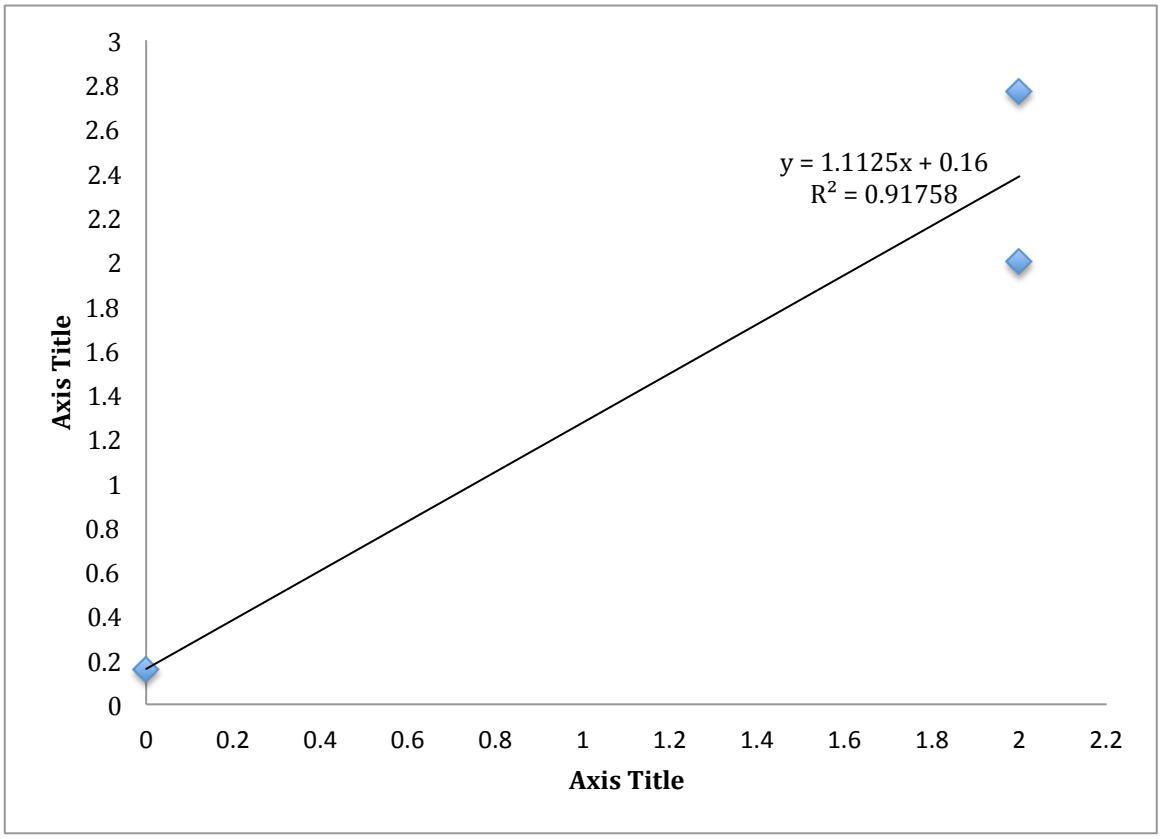


FIGURE 7

MUSE SCALE

17 participants completed the study and had MUSE scale results by the end of data collection. The MUSE scale results were calculated for each participant at baseline then at the end of study using the MUSE scale assessment tool (Cameron et al., 2010). The difference between the score for each participant was subtracted to determine what the change in each score was from baseline to end of study.

An independent t-test was performed on the difference of the MUSE Scores from baseline to end of study, the t-test was stratified by intervention group. It was assumed that the MUSE Scale difference would be significantly different between the two arms from baseline to end of study. The t-test results were performed on 10 participants in the intervention group and 7 participants in the control group. For the intervention group arm the mean of score difference was 0.7, SE= 1.39, SD= 4.40 (Table 6). For the control group arm the mean of the score difference was 1.86, SE=1.21, SD= 4.99 (Table 6). The alternative hypothesis Ha: diff>0, where Pr (T>t)= 0.67, t (15)= -0.46 (Table 6). All confidence intervals cross zero, making the results non-statistically significant.

TABLE 6: T-TEST OF THE DIFFERENCE IN MUSE SCALE RESULTS FROM BASELINE TO END OF STUDY BY INTERVENTION GROUP

	Number of Participants	Mean	SE	SD	95% CI
Intervention Arm	10	0.7	1.39	4.40	-2.4 – 3.85
Control Arm	7	1.86	2.28	6.04	-3.73 – 7.44
Combined	17	1.18	1.21	4.99	-1.39 – 3.74
Difference		-1.16	2.52	-	-6.53 - 4.21

Difference= mean (intervention) – mean (control)
Degrees of freedom=15
t=-0.46
Ha: diff <0, Pr (T<t)=0.33
Ha: diff=0, Pr (|T|<|t|)=0.65
Ha: diff>0, Pr (T>t)=0.67

TABLE 6

PARTICIPANT SATISFACTION

Qualitative information was collected for both participants in the control and intervention arm as the poster presented by a co-investigator, KS(Smith, 2012). The survey asked about the complexity of the regimen and those in the intervention arm were further asked about satisfaction questions regarding the pictorial medication calendar tool. The RCT survey did not ask care providers such as nurses or physicians on the perceived efficacy of the pictorial calendar tool as this data was collected previously.

COMPLEXITY OF TREATMENT REGIMEN

17 participants had final results available for the MUSE scale, with 10 participants, 58%, in the intervention arm and 7 participants, 41%, in the control arm. Of the 17 participants for which results were available for the MUSE scale, 8 participants in the intervention group and 3 participants in the control group completely disagreed that the medication regimen was complicated, 1 participant in the intervention group and 2 in the control group moderately disagreed, none of the participants neither agreed nor disagreed, 1 moderately agreed and 2 moderately agreed and no participants completely agreed (Figure 8).

FIGURE 8: SURVEY QUESTION "I FIND THE MEDICATION TREATMENT COMPLICATED"

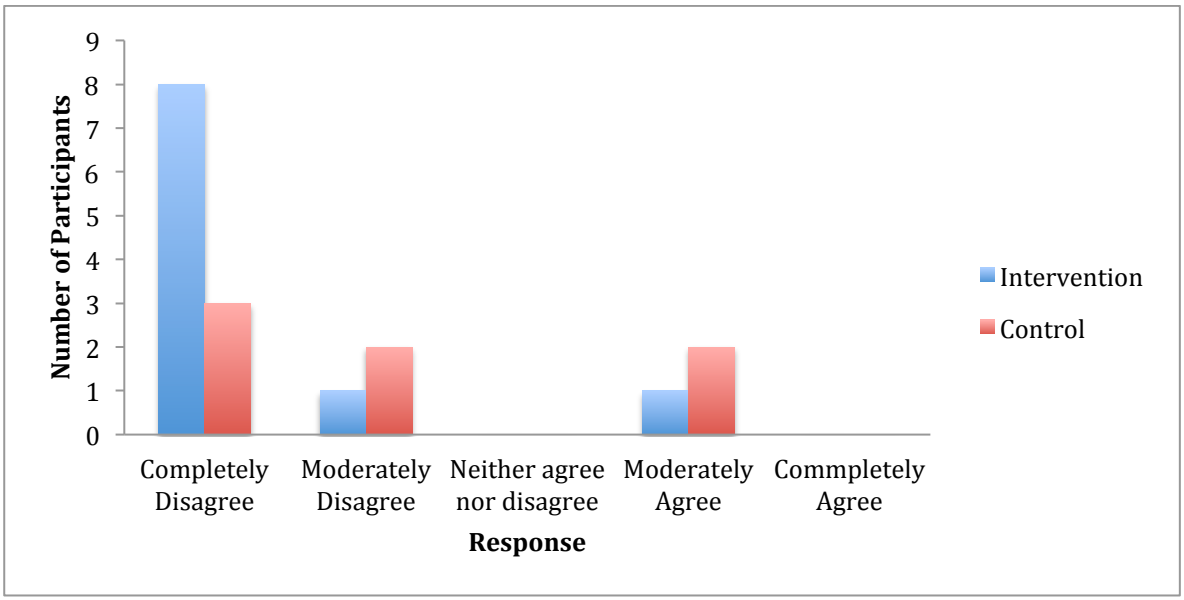


FIGURE 8

The remainder of the satisfaction survey questions that were answered on a Likert scale (Figure 9) were only targeted towards the intervention arm participants to assess their satisfaction with the pictorial calendar.

I USE THE STUDY CALENDAR TO HELP ME KEEP TRACK OF MY MEDICATION (S)

Of the intervention arm participants who answered the question "I use the study calendar to help keep track of my medication(s), none of the participants completely or moderately disagreed, 1 neither agreed nor disagreed, 3 moderately agreed and 5 completely agreed (Figure 9).

THE LAYOUT AND PICTURES OF THE CALENDAR MAKE IT EASY TO UNDERSTAND

Of the intervention arm participants who provided a response regarding the question "the layout and pictures of the calendar make it easy to understand", 1 completely disagreed with it's ease of understanding, none moderately disagreed or neither agreed nor disagreed, 3 moderately agreed and 5 completely agreed (Figure 9).

WHAT MEDICATION (S) YOU NEED TO TAKE

Of the intervention arm participants who provided a response to the question "did the calendar help you with what medication(s) you need to take", 1 participant indicated completely disagree, none moderately disagreed, 3 neither agreed nor disagreed, 1 moderately agreed and 5 completely agreed (Figure 9).

WHEN YOU NEED TO TAKE YOUR MEDICATION (S)

Of the intervention arm participants who answered the question "did the medication calendar help you decide when you need to take your medication(s)", none completely disagreed or moderately disagreed, 1 neither agreed nor disagreed, 3 moderately agreed and 5 completely agreed (Figure 9).

HOW MANY TIMES YOU NEED TO TAKE YOUR MEDICATION (S)

Of the intervention arm participants who answered the question "did the medication calendar help you with how many times you needed to take your

medication(s)", none answered completely disagree or moderately disagree, 2 neither agreed nor disagreed, 2 moderately agreed and 6 completely agreed (Figure 9).

FIGURE 9: SURVEY QUESTIONS FOR INTERVENTION (CALENDAR) ARM

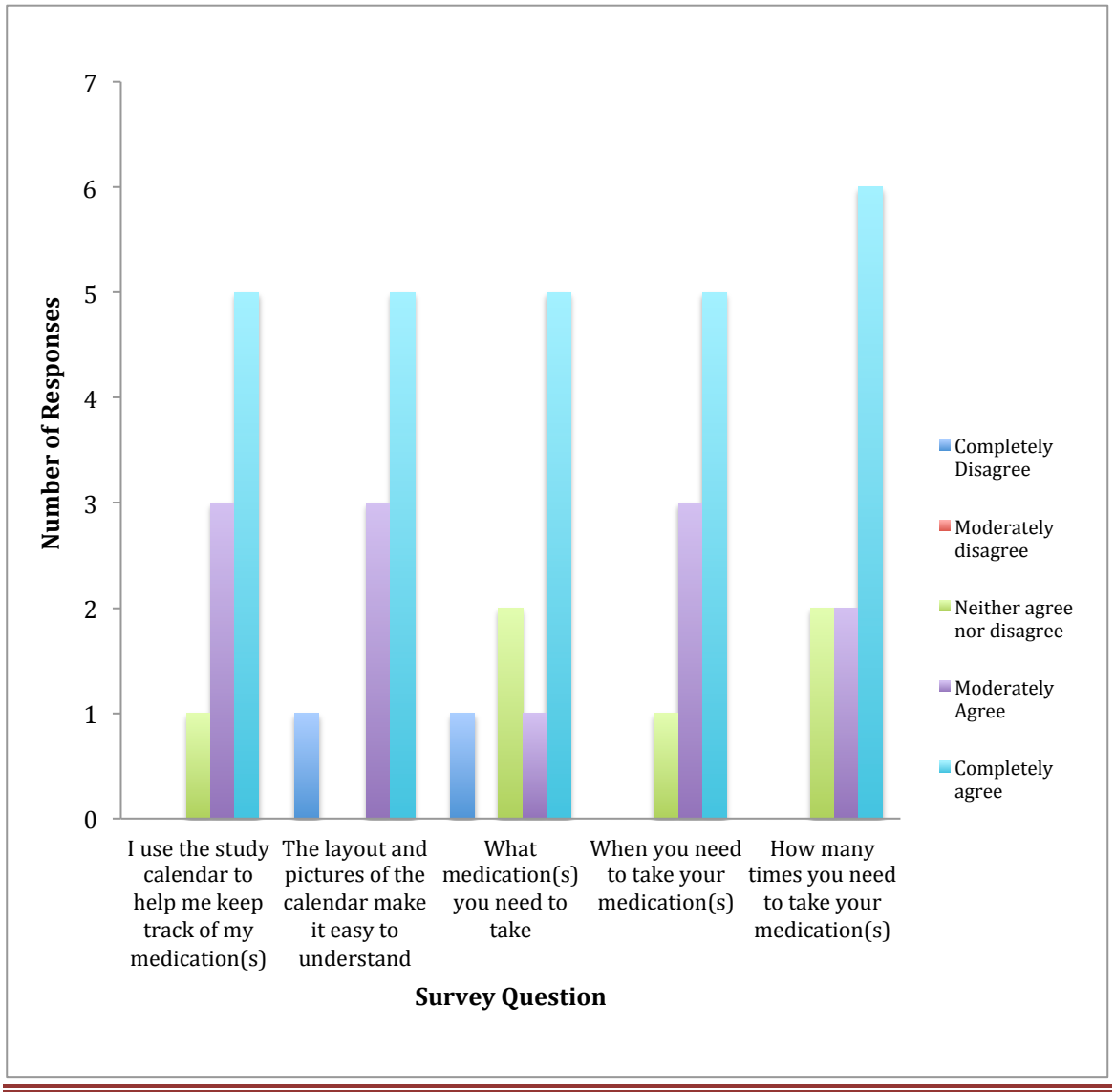


FIGURE 9

DISCUSSION

The initial study population involved adjuvant and neo-adjuvant breast cancer patients as well as adjuvant colon cancer patients. Due to the large proportion of breast cancer patients being female, the majority of the initial participant pool consisted of female patients, therefore that may be why of the 17 participants enrolled, 11 were female. Adherence as previously discussed may be affected by gender, whereby two studies have found that adherence tended to be better in males than females. Therefore, if a disparity in gender consists after full data collection, gender must be analyzed as confounder.

After the first 3 months of conducting the study, a request was sent to the Boards of Ethics at Waterloo and Western Universities to request expansion of the study to all adjuvant and neo-adjuvant solid organ, or non-hematologic malignancies to improve enrollment. The final proportions of male to female demographics may therefore change as the study proceeds.

The average age in both populations was relatively similar whereby the average was 57 and 63 years of age in the intervention and control group, respectively. Therefore, age as a confounding factor in adherence is not as likely in this population, however an analysis of age as confounder was not performed due to the small sample population. A multivariate analysis will be considered at final data analysis, if required.

It must be noted that most adherence studies in the literature that utilize pictorial based regimens or visual aids tended to target populations of lower literacy, however, our study population tended to have higher literacy with all participants at least attaining a

high school education. The statistics in the literature regarding the use of visual aids to improve adherence may therefore not be entirely applicable secondary to the difference in education level at baseline.

The difference in the number of medications taken outside of their oncology regimen on a daily basis may affect adherence. Participants in the intervention arm took approximately 20% less medications than those in the control arm. Pill burden has been previously associated with reduced adherence (Morrow et al., 1988), therefore that may need to be taken into consideration during final data analysis as a confounding variable if this trend persists.

The number of times that participants took medications that are not related to their oncologic regimen per day was very similar between the two groups, which reduces pill burden and number of times that a participant must remember to take medications per day. Therefore, adherence between the two groups would not have been affected by a confounding variable of number of times that medications were taken per day.

Two measures of adherence were utilized in the study including a pill count performed by pharmacy staff members that looked at the difference of pills given at baseline to pills remaining in vials after each cycle and also a subjective diary in which participants were to record the number of anti-emetics taken.

The calculation of self-reported adherence that was planned on being used was not utilized due to the low numbers of enrolled participants that completed the pill count. Therefore, this percentage of adherence will be revisited once the full study is complete and 174 participants have been enrolled.

A correlation analysis was performed to determine the relationship between scheduled pills taken as per the pill count performed by pharmacy staff and that, which was reported by the patient as per the recording in the diary. 11 out of 17 participants brought back their diaries, therefore only those participants' data points could be analyzed. The p value, was not statistically significant, however there did appear to be a trend towards significance, with the p value being slightly above 0.05 and the correlation statistic, r being 0.5976. Therefore with a larger sample size, this correlation may present differently.

Another correlation test was also to determine if there was a relationship between scheduled pills dispensed to the number of pills taken as per pill count and as per the diary. Since participants are intended to take all their scheduled anti-emetics, the expected correlation would be 1. The correlation between scheduled pills dispensed and scheduled pills taken, as per pill count was statistically significant with $p<0.01$ and the correlation statistic was 0.9613. This means that there is a strong relationship, which is almost 1 to 1 between the number pills taken and the number prescribed pills according to pill counts.

The correlation between scheduled pills dispensed and scheduled pills taken as per the diary was also statistically significant at $p<0.05$, and correlation coefficient was 0.7060. Therefore, it appears that the overall study population took scheduled anti-emetics as prescribed. At this point there is a trend towards a moderate relationship between the number of taken medications according to pharmacy pill count and recording of similar information into the diary logs.

One outcome that appeared to be different between both arms was the compliance with pill counts. Participants in the control arm were less complaint with pill counts than those in the intervention arm. 4 of the 7 participants in the intervention arm that were dispensed scheduled medications did not return the medications for a pill count, in contrast 2 of the 10 participants in the intervention arm did not return scheduled antiemetic medications for a pill count.

The lack of compliance with pill count could indicate that compliance was poorer for the participants in the control arm in general outside of study environment. At this point this difference may just be chance as it is not statistically interpreted and is simply an observation of the data.

A spearman's correlation analysis was performed to determine if there was a relationship between the total number of PRN antiemetic pills dispensed and the average symptoms of nausea and vomiting that participants experienced.

Of the 17 participants who completed the study, 7 did not return a diary and therefore average symptom score of nausea and vomiting could not be calculated. Therefore, according to STATA, 9 study participants could be analyzed. The correlation between PRN pills taken as per pill count and the symptoms recorded in the diary were not statistically significant, however the p value was close to 0.05 and the correlation coefficient, r=0.6471, in comparison the p value was much greater than 0.05 and correlation coefficient, r=0.2785 between the pills taken as per the diary and the average symptom score. This can be interpreted to mean that the there is a moderate positive

relationship between the number of pills taken according to pharmacy count and the severity of symptoms.

Therefore, it appears that at this point in time that there is a stronger correlation between pill counts performed by pharmacy staff and the participant's recorded symptoms than there are with the diary, however, due to the low number of diaries returned, a larger sample size will be required to determine if the diary is a poor tool for assessing concordance.

A regression analysis was also performed to determine if symptoms of nausea and vomiting could predict anti-emetic medication use. There did appear to be a statistically significant correlation between the PRN medication use in the intervention arm, as reported by pill count, and symptoms of nausea and vomiting, however this prediction could not be made for the pill count reported as per the diary. It would seem, according to the regression trend and the pill count that as the severity of symptoms increased, the number of pills taken according to pill count also increased. According to the preliminary regression analysis, symptoms account for approximately 71% of the variation in number of medications taken according to pill count.

Due to the low number of participants in the control arm, a regression analysis was not possible. A part of the reason why this may be the case is that many participants actually forgot to bring in their PRN anti-emetic vials and generally only brought in the scheduled anti-emetic empty vials. In order to determine if the calendar affects the participant's ability to use their PRN anti-emetics as prescribed in accordance with their symptoms, further data collection will be required.

According to the MUSE Scale author, only fully completed scales are analyzable and a score cannot be attained if the participant has elected not to answer a question (Cameron et al., 2010).

For the 17 participants who completed the MUSE scale both at baseline and at end of study, a independent sample t-test was performed on the difference of the MUSE Scores from baseline to end of study. The mean MUSE Scale score difference of observation in the intervention arm was 0.7 and for the control arm the mean MUSE Scale score difference was 1.86. Neither arms appeared to have a significant difference in results from baseline to end of study, $p=0.6735$.

The MUSE scale results between the intervention and control arm did not appear to be significantly different. Therefore, at this point it cannot be assumed that medication use and self-efficacy, according to the MUSE scale evaluation, is improved with the use of the calendar. With an increase in sample size, it will become clearer whether there is a difference in participant confidence and comfort with medication use and whether this medication use behaviour changes more or less from baseline to end of study.

It was anticipated that participants in the intervention arm would have less of a change in score from baseline to end of study due to the increased comfort with their medication regimen when given the calendar.

A confounder to this outcome may be that participants were at times randomized, consented and completed the MUSE scale before being counseled in pharmacy, therefore that would affect how comfortable participants felt at that point.

Subjective information from the participant point of view was collected regarding how complex each individual felt regarding their treatment regimen. This question was asked to both study arm participants. Participants in the control arm found the treatment regimen less complicated overall. The pictorial medication calendar tool may have played a factor in this response as those in the intervention arm would have not only been given routine care, but also would have received further information from the pictorial medication calendar.

Participants in the intervention arm were then asked a series of questions regarding the pictorial medication calendar. 9 participants in the intervention arm answered the survey questions. For the question, which asks whether the participant uses the study calendar to help them keep track of medications, the responses were mainly positive whereby 89% of participants either moderately or completely agreed that the tool helped them keep track of their medications.

When asked about whether the layout made the regimen easy to understand, 89% either moderately agreed or completely agreed and 1 completely disagreed. Therefore, the majority of participants felt that the layout was appropriate for ease of understanding of medications to be taken for nausea and vomiting in the setting of their oncologic regimen.

When asked about what whether the calendar helps participants know what medications to take 67% of participants moderately or completely agreed and the remainder of the participants, 23%, felt impartial to the tool's use for this purpose.

Lastly, when asked regarding whether the tool helped participants know when to take their anti-emetic medications, 98% of the participants either moderately or completely agreed that the tool was useful.

Therefore, it appeared that the calendar was a useful tool, subjectively to participants involved in the study for ease of medication use. Furthermore, it also appears that participants who received the diary felt that their regimen was less complex.

A planned interim analysis of the data is discussed herein for the purpose of a Masters Thesis. The full study is intended to have a sample size of approximately 174 participants. Data herein may not be statistically significant and may change overtime as the sample size increases. An increase normalization of distribution and increased analyzable data is expected upon study completion. The authors are aware that statistical significance or lack thereof at this point is difficult to prove, but the data provides a preliminary analysis.

The MUSE scale was utilized to determine if comfort with medications improved or changed between the two intervention arms from baseline to the end of the second cycle of chemotherapy. During the study, some participants were consented to the study before being counseled by a pharmacist and others were first counseled on anti-emetics given prior to chemotherapy, such as aprepitant and granisetron, the consented to the study. This may affect baseline MUSE results since patients may either feel more overwhelmed with information or feel more prepared for their chemotherapy when given further instructions. This confounder was difficult to control for as CRU staff may be able to speak with eligible candidates before entering the chemotherapy suite, such as at a

clinic visit or when the participant is at the centre to begin treatment, such as the first day of their first cycle.

Another important limitation to the willingness to participate in the study is a participant being counseled before or after consenting. At times it appears that when patients come to the pharmacy, they have been given a large amount of information and already want to return home. Therefore, the timing of interaction with the possible candidate may have affected willingness to participate in the study.

On multiple occasions, study participants have indicated to investigators that the medication diary utilized to determine adherence was a helpful tool in ensuring that the patient remembered to take their medications. Although this is a positive outcome with potential for further investigation, it was to act as a control between both the intervention and control arm, therefore the involvement of this tool as a factor that affects adherence was not accounted for when the study was created. Therefore, the use of the diary as an adherence tool may have acted as a confounder in improving adherence in both arms, which should become equal in both groups secondary to randomization.

Also, although nursing education occurred at baseline, there were multiple requests for calendars for participants on the study as the nurses also use the calendar to explain the anti-emetic regiment to patients. Therefore, participants on the control arm may have inadvertently received a calendar without the knowledge of study personnel. Further education occurred of the nursing staff regarding the study process and protocol after this issue was brought to the attention of an investigator.

Participants included information in the diary that was not related to just anti-emetic medication records and symptoms of nausea and vomiting. Information regarding symptoms such as pain, palpitations and constipation were also recorded. Therefore, all entries were inputted into REDCap, but only relevant information to nausea and vomiting was analyzed.

CONCLUSION

The use of a picture based medication calendar to improve the outcomes of adherence, concordance and self-efficacy, calculated by the MUSE Scale, have yet to be determined due to small sample size reported in this interim analysis. Participants that received the calendar appeared to find it useful for medication taking behaviours, with approximately 80% of participants either moderately or completely agreed that the diary helped them keep track of medications, helped with which medications to take, when to take them and how many times per day. We would recommend continued use of the calendar as an adjunct tool to routine care due to increased positive feedback regarding the tool and its layout; however, in order to validate the primary outcome of efficacy, a larger sample size will be required to provide a more objective outcome.

Before determining if this tool is valid and should be applicable to all chemotherapeutic regimens at the LRCP as a standard of care, determining whether primary outcome of improved adherence is statistically significant would need to occur. Therefore, approximately 140 participants still need to be enrolled to determine whether there is quantitative significance to the tool.

Furthermore, participant satisfaction with the tool must be taken into consideration as a strong variable in use of this tool as part of the standard of care. If the tool does not affect adherence as a primary outcome, but participants feel that it affects their medication use behaviour in a positive manner, then quality of life measure for anxiety due to complexity of medication regimen would need to be assessed to determine if this is a significant aid.

The continued use of this tool in the meantime as an adjunct is appropriate as the tool has shown subjectively, from the participant point of view, that it is useful and provides positive medication use behaviour.

FUTURE DIRECTIONS

SCOPING REVIEW

A scoping review of the literature since the Katz Review published in 2006 (Katz MG, 2006) will be performed with the primary objective of determining if there is existing literature on the use of visual aids for improvement of medication taking behaviours to better guide structuring of visual aids to improve medication adherence.

The scoping review will be done by two independent reviewers of the following databases: PUBMED, EMBASE and Cochrane. All the selected articles will have references reviewed for further applicable studies.

The scoping review will allow for further information to be gathered on literature available on adherence with a larger focus on qualitative literature, if applicable.

NURSING AND PHARMACIST WORKLOAD

Due to the complexity and breadth of the project, data regarding pharmacist and nursing workload could not be gathered. Therefore, this data will be assessed separately from the Master's Thesis. Workload will be measured by comparing the number of nursing callbacks and pharmacist time spent at the patient counselling and education session.

Workload data will be analyzed using a scatterplot and a line of best fit, if applicable, for number of minutes spent counselling participants or contacting participants for any reason related to medication use. For example, the adherence rate can be plotted against

the amount of time a pharmacist spends to see if a relationship exists. Similar analysis will be performed with the number of callbacks and patient adherence.

PARTICIPANT INVOLVEMENT

Participant involvement in improvement of the tool before dissemination to other disease sites and possibly centres would be required to ensure that patient input, which is highly valuable in development of adherence tools is sought. Focus groups would be required to ensure that patient advocates are able to provide feedback on the tool after its use. Also, anonymous questionnaires would be another useful tool to allow for participants to give feedback on the tool without creating bias.

LETTER OF COPYRIGHT PERMISSIONS

An email from the MUSE Scale tool author, Dr. Kenzie Cameron, was received on Wednesday July 10th 2015, which allowed us, the co-investigators, to utilize it for the purpose of the Calendar Study project.

The Open Access Journal, in which the tool was validated, did not return our email requesting permission to utilize the MUSE Scale.

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APPENDIX A: INFORMATION AND CONSENT FORM

London Regional Cancer Program
Calendar Project
LETTER OF INFORMATION AND CONSENT

Study Title
A Picture is Worth a Thousand Words: A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviour.

Primary Investigator

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Name of Sponsors

This centre is receiving funds from [Source A] and [Source B] to help offset the costs of conducting research.

Data provided to the sponsors will include:

- Project budget and expenses,
- Timeline for project completion,
- Updates about progress,
- Anticipated project completion date,
- Publication and presentation of results,
- Final report along with final disbursement request.

Conflict of Interest

- [Study Co-Investigator], designed the calendar and may be one of the pharmacists in your circle of care.
- [Study Co-Investigator], a medical oncologist, is one of the doctors involved in the study.
- [Study Co-Investigator] is a Pharmacy Resident and Masters Student. This research is part of the requirements for her education programs.

Introduction

You are being invited to participate in this research study about the use of a calendar designed to help patients take their medications. You are being invited because you are an adult patient (18 years of age or older) getting neoadjuvant or adjuvant chemotherapy treatment for breast cancer or adjuvant chemotherapy treatment for colon cancer. In this Consent document, "you" always refers to the study participant.

Background and Purpose

Even though cancer treatments are advancing, medications have also become more complex. Information can be a lot to remember for patients and care providers, they differ in shape, size, colour, generic name, brand name, and instructions for use. Therefore, it is not surprising that patients are often confused about how to take their medication. Patients must not only understand the regimens and side effects for their chemotherapy but also which supportive care medications are to be taken and when for symptoms such as nausea or vomiting. In this study, a calendar is being proposed to help patients take their medications. We also wish to assess whether the use of this medication calendar will improve concordance with prescribed supportive care medication regimens, improve patient satisfaction, improve quality of life and/or alleviate workload hours for pharmacy and nursing staff.

You are being asked to participate because you are an adult patient receiving neoadjuvant or adjuvant chemotherapy treatment for breast cancer or adjuvant chemotherapy treatment for colon cancer.

The usual treatment or standard of care for your disease:

At the [Study Centre], when the decision is made to start cancer treatment, baseline tests and scans are done depending on the treatment goals. Laboratory tests are also done at each follow-up visit. The number of follow-up and laboratory tests can vary depending on the treatment.

Once the first day of chemotherapy is started, usual care involves the oncology pharmacist explaining the use of your supportive care medications. You then have the opportunity to ask questions during the counseling sessions or by contacting the pharmacy as questions come up about the medications. You can also speak with the nursing staff or physicians. You will also receive a "My Care" binder that has information about which care provider to contact and when. This information can also be found at the London Regional Cancer Program website.

What will be Administered Outside of the Standard of Care for this Research Study?

The oncology pharmacist will counsel you about your supportive care medications. Participation means you will be randomly assigned to one of two groups. You will either be given a calendar along with usual care (group 1) or usual care alone (group 2). Both groups will have their medication schedules explained by the pharmacist and will have the chance to ask questions.

You will be asked to take a survey at the end of the second cycle of chemotherapy treatment about the study. Some personal health information including [hidden] will be kept is discussed in a section below.

Information that may affect how medications are taken including: length (in days) of each cycle for first two cycles of cancer treatment where supportive care medications are needed, number of times per day that supportive care regimen medications are to be taken on a scheduled or as needed basis and number of pills taken each time will be collected. Information on other medication regimens will be collected. You will be asked to determine the number of prescribed and non-prescribed medications (including supplements and vitamins) on the survey completed at the end of the second cycle of chemotherapy.

The number of people to participate:

Up to 174 people will participate in this study at [Study Centre].

The length of the study:

It is expected that you will be in the study for your first two cycles of chemotherapy.

Study Design

This is a randomized, open label study. An open-label study is one where the participants and investigators know what arm of the study you are in. If you decide to participate, you will be "randomized" into the usual treatment/standard of care or intervention arm. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor your doctor can choose what group you will be in. You will have a 1 in 2 chance of being placed in either group. You, your doctor and your circle of care at the [Study Centre] will know which intervention you are receiving.

Please see background and purpose for usual treatment or standard of care. The intervention arm will receive a calendar to be explained by the oncology pharmacist. Please see the "*What will be Administered Outside of the Standard of Care for this Research Study?"* section for further information regarding the study process.

Inclusion and Exclusion Criteria:

You will be asked to participate if you are an adult patient receiving chemotherapy treatment for non-metastatic neoadjuvant or adjuvant solid organ cancer. Only patients able to give consent for themselves will be asked to participate. A minimum grade 8 education and fluency in the English language is needed. If you are unable to repeat instructions back to research personnel, or become confused as time goes on while in the study, and someone else must speak on your behalf, you will be removed from the study. If you have trouble swallowing, or have problems seeing the calendar you will be excluded from the study. If you plan to receive multiple cycles of chemotherapy at a different site other than the LRCP will be excluded because it would be difficult to follow-up. If you have a speech or hearing impairment, you will be given the opportunity to participate in this study.

Procedures

- Study personnel will use a checklist to decide if you are eligible for the study. If you are eligible, you can enroll in this study up to the day of your first chemotherapy treatment.
- [Hidden] will be recorded, even for ineligible individuals or those that refuse to participate to ensure that participants are not contacted more than once.
- A randomization process will be used to place you in the intervention or control arm.
- During the first chemotherapy visit, you will be asked to complete a Medication Understanding and Use Self Efficacy Scale (MUSE).
- During your first chemotherapy visit, an oncology pharmacist will speak to you about your supportive care medication prescriptions.
- You will be given a diary to track information about the medications taken:
    - Date, time, name of supportive care medication taken, number of pills taken,
    - Reason for taking the supportive care medication (e.g., nausea),
    - A space for rating of symptoms.
- If you are randomized to the intervention arm, you will also be given a calendar, to be explained by the oncology pharmacist.

- At the end of the second cycle of chemotherapy, you will be asked to bring in your supportive care medication vials. A pill count will be done and the information will be recorded for the study.
- At the end of the second cycle of chemotherapy, you will be asked to fill out a survey about the study. Some information about you and medications you take will be collected.
- At the end of the second cycle of chemotherapy, you will be asked to complete another MUSE scale. You will also be asked to return your diary.
- No extra visits will be needed for this study.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study or to be in the study now and change your mind later. You may leave the study at any time without affecting your care. We will give you new information that is learned during the study that might affect your decision to stay in the study. You may refuse to answer any question you do not want to answer, or not answer an interview question by leaving the answer blank or if a verbal questionnaire is done; you may say, "pass".

Withdrawal from Study

If the researcher decides to withdraw you from the study:

The researchers can take you off the study for reasons such as:

- Change of supportive care regimen during two cycles of chemotherapy,
- If you are unable to repeat instructions, become confused as time goes on, or if someone must speak on your behalf.

If you request to be withdrawn from the study:

- The information that was collected before you leave the study will still be used to help answer the research question, including de-identified demographic information, information from questionnaires and surveys completed during the study, diary information and pill counts.
- If you wish to remove any information collected about you from the study, please contact [Co-Investigator], co-investigator within 30 days of the start of participation in the study and every effort will be made to ensure that all data collected during the study is withdrawn. This will allow for your information to be removed prior to data analysis. Please find contact information at the end of this document.
- No new information will be collected without your permission.

Risks

- If you depend on the calendar and misplace it, you may have trouble taking medications.
- There is a small risk that there could be a mistake on your medication calendar or that you may receive an incorrect calendar. However, the pharmacist reviewing your supportive care regimen will guide you on the use of the calendar, therefore the risk of receiving an incorrect calendar or an error not being caught will be minimal.
- You may experience psychological risks such as anxiety, distress, or feelings of sadness when asked questions about sensitive issues (e.g., nausea and vomiting).

Benefits

Benefits to patients:

- May improve medication-taking behaviours.

Benefits to society or science:

- May help to alleviate workload for staff.
- May expand to management of medications for other medical conditions.
- You may wish to share with other caregivers involved in your care.

You may not receive direct benefit from being in this study. Information learned from this study may help lead to improve medication taking-behaviours in the future.

Reminders and Responsibilities

Please remember that it is your responsibility to keep track of your diary and write in it when you take a supportive care medication for your treatment. Therefore, if you enroll in another study during the course of this calendar project, please tell a study team member.

Alternatives to Being in the Study

An alternative to being in the study is to continue on just as you do now.

Confidentiality

Protection of participant privacy:

Paper information that is collected that identifies you will be stored in a locked cabinet in the [Hidden]. All data outside of the master list and consent forms will be kept anonymous with your name changed into an alphanumeric code. Hardcopy data that have been de-identified will be entered into an electronic database and be stored at [Hidden] or on an encrypted USB stick.

Access to your records will be limited to the authorized personnel on the research team at [Hidden].

Personnel with access to study information and extent of access:

[Hidden]

Personal health information to be collected and length of time retained:

Demographic information: [Hidden], initials, gender and age. A list linking your study number with [Hidden] will be kept by the study personnel in a secure place, separate from your study file. Information about medications taken for chronic illnesses (such as high blood pressure) and how many other pills are taken per day will be collected. You will be asked about the number of prescribed and non-prescribed medications you take.

Identifiable information will be put in confidential shredding bin or deleted 1 year from the date that data collection ends for this project. Primary data documents (such as the diary, surveys and questionnaires) that have been de-identified will be stored at [Hidden] for 15 years in keeping with [Hidden] requirements and then be placed in the confidential shredding bins. Data that has been de-identified and transferred to an electronic format for analysis will be retained for 15 years and then erased.

Who, outside of study team, will have access to de-identified information?

Qualified representatives of the following organizations may look at your medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines:

[Hidden]

All identifiable information collected during this study, will be kept confidential and will not be shared with anyone outside the study unless required by law. Participants will not be named in any reports, publications, or presentations that may come from this study.

Costs

You will not have to pay for the diary, surveys or calendar involved with this study. You will not be reimbursed for transportation, meals, time or inconvenience.

Compensation

You will not be compensated for participating in this study.

Rights as a Participant

You do not waive any legal right by signing this consent form.

Commercialization

Study personnel and/or others intend to claim sole ownership of any research results consistent with this consent. By signing this consent, you agree that study personnel can apply for patents and you will not receive any financial benefit that might come from the research.

Questions about the Study

You can contact [Hidden], regarding any questions or concerns that may be raised by participating in the study or questions that may be raised by being a research participant.

[Study Co-Investigator's Contact Information is hidden]

If you have any questions about your rights as a research participant or the conduct of this study, you may contact:

[Hidden]

London Health Sciences Centre
London Regional Cancer Program

Consent Form

Title of Project: A Picture is Worth a Thousand Words: A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviour.

Names of Researchers: [Hidden]

You are being invited to participate in this randomized, open label study to assess medication taking-behaviours because you are an adult patient (18 years of age or older) receiving neoadjuvant or adjuvant chemotherapy treatment for breast cancer or adjuvant chemotherapy treatment for colon cancer. The study will take place at the [Hidden], and it is expected that you will be in the study for your first two cycles of chemotherapy.

I confirm that I have read and understand the statement for the above study and have had the opportunity to ask questions.

Inclusion Criteria:

- ☐ Adult patient (18 years of age or older)
- ☐ Receiving chemotherapy treatment for non-metastatic:
  a. Neoadjuvant OR
  b. Adjuvant solid organ malignancy
- ☐ Able to give consent independently

Exclusion Criteria:

- ☐ Did not attain minimum of grade 8 education
- ☐ Non-English speaking
- ☐ Unable to repeat instructions to research personnel
- ☐ Difficulty swallowing
- ☐ Planning to receive multiple cycles of chemotherapy at alternate sites other than LRCP
- ☐ Significant visual impairment

I understand that my participation is voluntary and that I am free to withdraw at any time.

I agree to take part in the above study.

_____	_____	_____
Name of Participant	***Date***	***Signature***
_____	_____	_____
Research Personnel	***Date***	***Signature***

APPENDIX B: FEEDBACK LETTER

London Health Sciences Centre
London Regional Cancer Program

University of Waterloo

Date: _____

Dear Study Participant:

I would like to thank you for your participation in the study "A Picture is Worth a Thousand Words". You were invited to participate in this research study about the use of a calendar designed to help patients take their medications.

The data collected for this study will help us to understand how a picture-based medication calendar helps patients take their medications. This study included adult patients receiving treatment for solid organ cancers. This calendar may be used for patients with other medical conditions in the future.

Please remember that every effort will be made to make sure that any personal data we collected about you is protected. Once all of the data are collected and reviewed, we plan to share this information with other healthcare workers through seminars, conferences, presentations, and journal articles.

If you are interested in receiving information about the results of this study, please provide your email address to [Hidden]. When the study is completed [Hidden] will send you a summary of the results. If you have any questions about the study at any time, you can contact [Hidden] by email or telephone.

As with all [Hidden] projects involving human participants, this project received ethics approval through [Hidden] Research Ethics Committees.

Should you have any comments or concerns resulting from your participation in this study, please contact:

[Hidden]

Please direct any general questions to the researchers below:

[Hidden]

Sincerely,

Mira Maximos,
Student Researcher

12-March-2017, Version 5

25-February-2017. Version 5

Researchers: Mira Maximos, Kelly Smith, Karin Hahn, Venita Harris, Feng Chang, Michael Miller, Jonathan Blay and Tom McFarlane.

A randomized, open label study to assess medication-taking behaviours. The study will be conducted at the London Health Sciences Centre, London Regional Cancer Program, and it is expected that participants will be in the study for the first two cycles of chemotherapy.

— METHODS —

A Picture is Worth a Thousand Words:

A Randomized Controlled Trial to Assess Medication Taking Behaviours

Inclusion Criteria

- ☐ Adult patient (18 years of age or older) at LRCP
- ☐ Receiving chemotherapy treatment for non-metastatic:
  - a. Neoadjuvant OR
  - b. Adjuvant solid organ cancer
- ☐ Able to give consent independently
- ☐ Be on at least one scheduled medication for management of nausea and vomiting

Exclusion Criteria

- ☐ Did not attain minimum of grade 8 education
- ☐ Non-English speaking
- ☐ Unable to repeat instructions to research personnel
- ☐ Difficulty swallowing
- ☐ Planning to receive multiple cycles of chemotherapy at alternate sites other than LRCP
- ☐ Significant visual impairment

FOR QUESTIONS, CONTACT:

Venita Harris Mira Maximos Kelly Smith

APPENDIX D: ACCOUNTABILITY LOG

London Health Sciences Centre
London Regional Cancer Program

Page No _____

SUPPORTIVE CARE MEDICATION ACCOUNTABILITY LOG

Date (DD/MM/YY)	Participant Study ID	Pill Count of Nausea and Vomiting Supportive Care Medications			Time Spent Counseling	Notes	Writer's Initials
		Medication Name	Number of Pills Dispensed	Number of Pills Remaning			

This document contains private information

If found, please return to:

[Hidden Data]

London Health Sciences Centre
London Regional Cancer Program

London Health Sciences Center, London Regional Cancer Program

A Picture is Worth a Thousand Words

Participant Diary

Participant ID: _____

2016 - 2017

Participant ID: _____

Instructions

Please **do not** record your name or personal information on any part of this diary.

Complete each page of the diary on a daily basis for the first two cycles of your chemotherapy treatment.

If no symptoms occur on a particular day, please record "not applicable" in the first section, under the list of supportive care medication(s) taken today.

Return this diary to the "***Calendar Project" study personnel*** or the ***London Regional Cancer Program Pharmacy*** on the last day of your second cycle of chemotherapy.

Date: _____

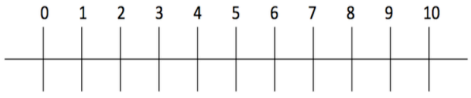
Check off the supportive care medication(s) taken today for nausea or vomiting and number of pills taken:

□ Aprepitant, # pills today: ____
□ Dexamethasone, # pills today: ____
□ Granisetron, # pills today: ____
□ Ondansetron, # pills today: ____
□ Prochlorperazine, # pills today: ____
□ Other: _____ , # pills today: ____

On a scale from 0 to 10, where **"0"** is ***no symptoms at all*** and **"10"** is the **worst possible severity of symptoms**, where do you rate the symptom(s) below. Circle a number on the scale below.

Symptom: _____

Severity:



Participant ID: _____

Date: _____

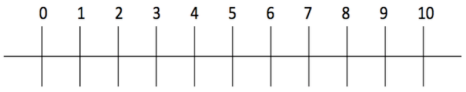
Check off the supportive care medication(s) taken today for nausea or vomiting and number of pills taken:

□ Aprepitant, # pills today: ____
□ Dexamethasone, # pills today: ____
□ Granisetron, # pills today: ____
□ Ondansetron, # pills today: ____
□ Prochlorperazine, # pills today: ____
□ Other: _____ , # pills today: ____

On a scale from 0 to 10, where **"0"** is ***no symptoms at all*** and **"10"** is the **worst possible severity of symptoms**, where do you rate the symptom(s) below. Circle a number on the scale below.

Symptom: _____

Severity:



Participant ID: _____

Date: _____

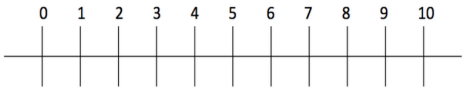
Check off the supportive care medication(s) taken today for nausea or vomiting and number of pills taken:

□ Aprepitant, # pills today: ____
□ Dexamethasone, # pills today: ____
□ Granisetron, # pills today: ____
□ Ondansetron, # pills today: ____
□ Prochlorperazine, # pills today: ____
□ Other: _____ , # pills today: ____

On a scale from 0 to 10, where **"0"** is ***no symptoms at all*** and **"10"** is the **worst possible severity of symptoms**, where do you rate the symptom(s) below. Circle a number on the scale below.

Symptom: _____

Severity:



APPENDIX F: STUDY SURVEY

London Health Sciences Centre
London Regional Cancer Program

CHEMOTHERAPY SUPPORTIVE CARE MEDICAITON CALENDAR: INTERVENTION

PLEASE TELL US ABOUT YOURSELF

□ Male □ Female Age:_____ Study Participant #: _____

Highest level of education you have completed: □ Grade School □ High School □ College □ University □ Post Graduate

Does someone help you take your medications? □ Yes □ No

PLEASE TELL US ABOUT YOUR CHEMOTHERAPY MEDICATIONS

When you take your medication(s), do you use: □ Instructions on pill bottle □ Other *(please specify):* _____

Do you use other reminders to help you take your chemotherapy related medications? □ Yes □ No
If YES, what do you use? □ Caregiver □ Alarm □ Blister Pack □ Calendar *(regular monthly type)* □ Other *(Please specify):*_____

Please rate the following statements:

	COMPLETELY DISAGREE	MODERATELY DISAGREE	NEITHER AGREE NOR DISAGREE	MODERATELY AGREE	COMPLETELY AGREE
• I find the medication treatment complicated	□	□	□	□	□
• I use the study calendar to help me keep track of my medication(s)	□	□	□	□	□
• The layout and pictures of the calendar make it easy to understand	□	□	□	□	□

Did the calendar help you better understand:

	COMPLETELY DISAGREE	MODERATELY DISAGREE	NEITHER AGREE NOR DISAGREE	MODERATELY AGREE	COMPLETELY AGREE
• What medication(s) you need to take	□	□	□	□	□
• When you need to take your medication(s)	□	□	□	□	□
• How many times you need to take your medication(s)	□	□	□	□	□

PLEASE TELL US ABOUT YOUR NON-CHEMOTHERAPY MEDICATIONS

How many different PRESCRIBED medications do you take that are not related to your cancer treatment (e.g. diabetes or blood pressure medications)?
Please specify a number: _____

How many different NON-PRESCRIBED medications do you take that are not related to your cancer treatment (e.g. herbal and over the counter products)?
Please specify a number: _____

How many times a day do you take medications that are not related to your cancer treatment?
Please specify a number: _____

Please hand in this survey to an LRCP pharmacy staff member to be added to the medication adherence calendar study box.

Last Updated August 2nd 2016

London Health Sciences Centre
London Regional Cancer Program

CHEMOTHERAPY SUPPROTIVE CARE MEDICAITON CALENDAR: USUAL CARE ARM SURVEY

PLEASE TELL US ABOUT YOURSELF

☐ Male ☐ Female Age:_____ Study Participant #: _____

Highest level of education you have completed: ☐ Grade School ☐ High School ☐ College ☐ University ☐ Post Graduate

Does someone help you take your medications? ☐ Yes ☐ No

PLEASE TELL US ABOUT YOUR CHEMOTHERAPY MEDICATIONS

When you take your medication(s), do you use: ☐ Instructions on pill bottle ☐ Other *(please specify):* _____

Do you use other reminders to help you take your chemotherapy related medications? ☐ Yes ☐ No

If YES, what do you use? ☐ Caregiver ☐ Alarm ☐ Blister Pack ☐ Calendar *(regular monthly type)* ☐ Other *(Please specify):*_____

Please rate the following statements:	COMPLETELY DISAGREE	MODERATELY DISAGREE	NEITHER AGREE NOR DISAGREE	MODERATELY AGREE	COMPLETELY AGREE
• I find the medication treatment complicated	☐	☐	☐	☐	☐

PLEASE TELL US ABOUT YOUR NON-CHEMOTHERAPY MEDICATIONS

How many different PRESCRIBED medications do you take that are not related to your cancer treatment (e.g. diabetes or blood pressure medications)?

Please specify a number: _____

How many different NON-PRESCRIBED medications do you take that are not related to your cancer treatment (e.g. herbal and over the counter products)?

Please specify a number: _____

How many times a day do you take medications that are not related to your cancer treatment?

Please specify a number: _____

Please hand in this survey to an LRCP pharmacy staff member to be added to the medication adherence calendar study box.

Last Updated August 2nd 2016

London Health Sciences Centre
London Regional Cancer Program

Randomization and Enrollment Form

"A Picture is Worth a Thousand Words:
A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviours.

Participant ID: (alpha-numeric code)	**Visit Date:** __ __ / __ __ __ / __ __ __ __ (d d m m m y y y y)

Visit Type: ☐ **Baseline** ☐ **Randomization**

Is the participant eligible for the study based on inclusion and exclusion criteria listed below (must meet ALL inclusion criteria and NONE of exclusion criteria)?

Inclusion Criteria:	**Exclusion Criteria:**
☐ Adult patient (18 years of age or older) ☐ Receiving chemotherapy treatment for: a. Neoadjuvant OR b. Adjuvant solid organ cancer ☐ Able to give consent independently	☐ Did not attain minimum of grade 8 education ☐ Non-English speaking ☐ Unable to repeat instructions to research personnel ☐ Difficulty swallowing ☐ Planning to receive multiple cycles of chemotherapy at alternate sites other than LRCP ☐ Significant visual impairment

Eligible:
☐ Yes
☐ No **(If no leave the rest of the form blank.)**

If yes:
1. Date enrolled (met all eligibility criteria):
__ __ / __ __ __ / __ __ __ __ (d d m m m y y y y)
2. Date randomized, if different from enrolled:
__ __ / __ __ __ / __ __ __ __ (d d m m m y y y y)

Or:
3. If eligible and not randomized, indicate reason:
☐ Failed to return ☐ Declined participation ☐ Other (specify): _____

Name of Study Personnel: _____

Signature of Study Personnel: _____

Date of Form Completion: _____

Adapted from Case Report Forms (Randomization and Enrollment Version 2.0. 24 April 2013) on the National Center for Complementary and Integrative Health Website.

Version 4 February 2017

APPENDIX H: PROTOCOL DEVIATION FORM

Protocol Deviation Tracking Log

Protocol ID/Number:	
Protocol Title (Abbreviated):	Pictorial Medication Calendar

Ref No.	Subject ID	Date of Deviation	Date Identified	Deviation Description	Dev. Type [A-J]	Resulted in AE?	Did Subject Continue in Study?	Meets IRB Reporting Req. (Yes/No)	IRB Reporting Date
1									
2									
3									
4									
5									
6									
7									

Co-Investigator Signature: _____ **Date:** _____

Adapted from Case Report Forms (Protocol Deviation Tracking Log Version 2.0. 24 April 2013) on the National Center for Complementary and Integrative Health Website.

APPENDIX I: VISIT CHECKLISTS

London Health Sciences Centre
London Regional Cancer Program

Study Initiation: Checklist for Intervention Arm

**"A Picture is Worth a Thousand Words:
A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviours.**

Pt_ID: _____

Date Completed:
__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

Did the participant attend this visit? ☐ Yes (if yes, continue) ☐ No

Please check all the study components completed below:

- ☐ Inclusion/Exclusion Eligibility Criteria
- ☐ Randomization and Enrolment
- ☐ MUSE questionnaire
- ☐ Diary provided
- ☐ Calendar given
- ☐ Patient counseled

Is the participant continuing in the study? ☐ Yes ☐ No

If no, remember to complete a STUDY COMPLETION form.

Comments:

Adapted from Case Report Forms (Visit Checklist Version 2.0) on the National Center for Complementary and Integrative Health Website.

Visit Checklist Version 2 October 2015

London Health Sciences Centre
London Regional Cancer Program

Study Initiation: Checklist for Control Arm

**"A Picture is Worth a Thousand Words:
A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviours.**

Pt_ID: _____

Date Completed:
__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

Did the participant attend this visit? ☐ Yes (if yes, continue) ☐ No

Please check all the study components completed below:

- ☐ Inclusion/Exclusion Eligibility Criteria
- ☐ Randomization and Enrolment
- ☐ MUSE questionnaire
- ☐ Diary provided
- ☐ Patient counseled

Is the participant continuing in the study? ☐ Yes ☐ No

If no, remember to complete a STUDY COMPLETION form.

Comments:

Adapted from Case Report Forms (Visit Checklist Version 2.0) on the National Center for Complementary and Integrative Health Website.

Visit Checklist Version 2 October 2015

London Health Sciences Centre
London Regional Cancer Program

Study Conclusion: Checklist for Intervention Arm

**"A Picture is Worth a Thousand Words:
A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviours.**

Pt_ID: _____

Date Completed:
__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

Please check all the study components completed below:

- ☐ Pill Count
- ☐ Return Diary
- ☐ MUSE questionnaire
- ☐ Study survey
- ☐ Feedback letter

Comments:

Adapted from Case Report Forms (Visit Checklist Version 2.0) on the National Center for Complementary and Integrative Health Website.

Visit Checklist Version 2 October 2015

London Health Sciences Centre
London Regional Cancer Program

Study Conclusion: Checklist for Control Arm

**"A Picture is Worth a Thousand Words:
A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviours.**

Pt_ID: _____

Date Completed:
__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

Please check all the study components completed below:

- ☐ Pill Count
- ☐ Return Diary
- ☐ MUSE questionnaire
- ☐ Study survey
- ☐ Feedback letter

Comments:

Adapted from Case Report Forms (Visit Checklist Version 2.0) on the National Center for Complementary and Integrative Health Website.

Visit Checklist Version 3 June 2016

London Health Sciences Centre
London Regional Cancer Program

Study Completion

**"A Picture is Worth a Thousand Words:
A Randomized Controlled Trial to Assess the Influence of a Pictorial Medication Calendar on Medication Taking Behaviours.**

Participant ID: (alpha-numeric code)	**Visit Date:** ___ ___ / ___ ___ / ___ ___ ___ ___ (d d m m y y y y)

1. Date of final study visit: ___ ___ / ___ ___ / ___ ___ ___ ___ (d d m m y y y y)

2. Primary reason for terminating participation in the study:

   ☐ Completed study

   ☐ Participant was determined after enrollment to be ineligible (provide comments): _____

   ☐ Participant withdrew consent

   ☐ In the principal investigator's opinion, it was not in the participant's best interest to continue (provide comments): _____

   ☐ Adverse event (If checked, complete the AE form.)

   ☐ Death

   ☐ Lost to follow-up

   ☐ Other (specify): _____

   ☐ Unknown

Comments:

_____

_____

_____

_____

Study Personnel Signature: _____ Date: _____

Adapted from Case Report Forms (Visit Checklist Version 1.0) on the National Center for Complementary and Integrative Health Website.

Version 2 October 2015

APPENDIX K: UNANTICIPATED PROBLEMS FORM

London Health Sciences Centre
London Regional Cancer Program

Unanticipated Problem (UP)

Protocol Name and Number:	Subject ID Number:
_____	_____

1. Date UP Identified: _ _/ _ _ _/ _ _ _ _ (dd/mmm/yyyy)
2. Identify UP:_____
3. The Unanticipated Problem was unexpected in terms of nature, severity, or frequency: ☐ Yes ☐ No
4. The Unanticipated Problem is possibly related to participation in the research: ☐ Yes ☐ No
5. The Unanticipated Problem suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized: ☐ Yes ☐ No

   If the answers to questions 3–5 are ALL "YES," report event as an Unanticipated Problem to Principal Investigator to forward to the institutional review board.

6. Briefly describe the UP. Attach additional pages or supplementary information as necessary. Include date of incident and date of discovery. Describe harm or potential harm that occurred to subject(s), whether the incident is resolved, and whether the subject(s) remains in the study:

7. What action was taken with the study as a result of the Unanticipated Problem? (Check all that apply.)

   ☐ No action
   ☐ Revise protocol to eliminate apparent immediate hazards to subjects
   ☐ Modification of inclusion or exclusion criteria to mitigate newly identified risks
   ☐ Implementation of additional procedures for monitoring subjects
   ☐ Suspension of enrollment of new subjects
   ☐ Notify currently enrolled subjects
   ☐ Suspension of research procedures in currently enrolled subjects
   ☐ Modification of consent documents to include a description of newly recognized risks
   ☐ Provision of additional information about newly recognized risks to previously enrolled subjects
   ☐ Other: _____

Adapted from Case Report Forms (Unanticipated Problem Version 1.0. 31 May 2013) on the National Center for Complementary and Integrative Health Website.

Unanticipated Problem (UP)

(continued)

8. Is the Unanticipated Problem a serious adverse event? ☐ Yes ☐ No

If the Unanticipated Problem is a serious adverse event, submit this form and complete the Serious Adverse Event form.

Statement of Principal Investigator: *I have personally reviewed this report and agree with the above assessment.*

_____ __ __/ __ __ __/ __ __ __ __
Signature of Co-investigator Date

_____ __ __/ __ __ __/ __ __ __ __
Name of Person Completing the Form Date

Adapted from Case Report Forms (Unanticipated Problem Version 1.0. 31 May 2013) on the National Center for Complementary and Integrative Health Website.