Remote Proactive Ambulatory Toxicity Management During Adjuvant or Neo-adjuvant Chemotherapy for Early Stage Breast Cancer - A Pragmatic Cluster-Randomized Trial

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The guarantor (MKK) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author (MKK) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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KEY MESSAGES BOX

- Emergency department visits and hospitalizations, common during cancer chemotherapy, may be preventable with adequate support between clinic visits however large-scale evaluations of remote management are limited.
- Proactive telephone-based toxicity management during chemotherapy did not lead to fewer emergency department visits or hospitalizations (mean number of emergency department visits and hospitalizations/patient, intervention: 0.91, SD=0.40; control: 0.94, SD=0.28, p=0.94), but was associated with fewer grade 3 toxicities than the control (48% vs 58%, p=0.028).
- With the rapid rise in remote care due to the COVID pandemic, identification of scalable strategies for remote management of patients during cancer treatment is particularly relevant.

ABSTRACT

Objectives: To evaluate the effectiveness of remote proactive management of toxicities during chemotherapy for early stage breast cancer.

Design: Pragmatic cluster-randomized trial.

Setting: Twenty cancer centres in Ontario, Canada allocated by covariate-constrained randomization to remote management or routine care.

Participants: All patients commencing adjuvant/neo-adjuvant chemotherapy for early stage breast cancer at each centre were included. A subset of 25 patients from each centre completed patient-reported outcome (PRO) questionnaires.

Intervention: Proactive, standardized, nurse-led telephone management of common toxicities at two time points following each chemotherapy cycle.

Main outcome measures: The primary outcome, cluster-level mean number of emergency department visits or hospitalizations (ED/H) per patient during the entire chemotherapy course, was evaluated using routinely available administrative health data. Secondary PRO outcomes included toxicity, self-efficacy and quality of life.

Results: Baseline characteristics of participants were similar in the intervention (n=944) and control arms (n=1214); 22% were older than 65. Penetration, i.e., the percentage of patients who received the intervention at each centre, ranged from 50-86%. Mean number of ED/H visits/patient was 0.91 (SD=0.40) in the intervention and 0.94 (SD=0.28) in the control arm (p=0.94); 47% of patients had at least one ED/H visit during chemotherapy. There were fewer patients with grade 3 toxicity in the intervention arm, 48% vs 58%, p=0.028. There was no

difference in self-efficacy. Intervention patients had a smaller decline in Functional Assessment of Cancer Therapy (FACT) Trial Outcome Index (-6.1 vs -9.0; difference=2.9, 95% CI, 0.8 to 5.0; p=0.008) and FACT Physical Well-being (-3.0 vs -4.6, difference=1.6, 95% CI, 0.7 to 2.5; p<0.001).

Conclusions and Relevance: Proactive telephone-based toxicity management during chemotherapy led to fewer grade 3 toxicities, but did not lead to fewer ED/H. With the rapid rise in remote care due to the COVID pandemic, identification of scalable strategies for remote management of patients during cancer treatment is particularly relevant.

Trial Registration: NCT02485678; clinicaltrials.gov

INTRODUCTION

Chemotherapy plays an important role in the management of many cancers but is associated with significant toxicity. Since the majority of chemotherapy is administered in ambulatory settings, patients who experience toxicities do so between visits to the cancer centre. Population-based studies suggest that acute care use, such as emergency department visits or hospitalizations (ED/H), are common during chemotherapy; [1-3] with as many as 42% of patients receiving systemic therapy in routine practice having at least one emergency room visit or hospitalization during treatment.[4] Many toxicities are predictable and may be preventable or ameliorated with earlier intervention. Consequently, acute care utilization and patient outcomes may be improved with effective proactive remote support between clinic visits.

Over the last decade, there has been substantial interest in identifying approaches to support patients with cancer receiving chemotherapy between visits to the cancer centre to minimize toxicity, improve quality of life (QoL), and decrease acute care utilization. Remote interventions such as telephone-based outreach[5-6] and mobile applications or devices[7-8] have shown promise in either early phase or proof of concept individually randomized studies. While large-scale evaluations of above interventions are currently in progress,[9-10] data on effectiveness and scalability of these types of interventions at a system level are limited. In our previous single arm two-institution study of a proactive, telephone-based outreach strategy which focused on toxicity management by trained oncology nurses in patients undergoing adjuvant chemotherapy for breast cancer, we showed that the intervention was feasible, acceptable to patients and providers, and associated with lower emergency department (ED) visits compared to historical controls.[11] We now report the effectiveness of remote proactive

management of chemotherapy-related toxicities in patients with early-stage breast cancer receiving chemotherapy in a multicenter pragmatic cluster-randomized trial (cRCT) wherein the primary outcome was evaluated using existing administrative health data.

METHODS

Study Design

We undertook a pragmatic cRCT to evaluate the impact of proactive, nurse-led telephone-based symptom management on the cluster-level number of ED/H per patient; the full trial protocol has been published previously.[12] Briefly, 20 cancer centres in Ontario, Canada were randomly allocated; 10 to proactive remote management (intervention) and 10 to routine care (control). Participants included all patients with early stage (stage I-III) breast cancer commencing adjuvant or neo-adjuvant chemotherapy at participating institutions during the intervention period. Patients receiving an investigational drug or treated exclusively with hormonal or targeted therapies were excluded.

Ethical Considerations

The intervention was introduced in the centres as a process change as per quality improvement principles hence individual written informed consent was waived.[13] For control centres employing their local standard of care, informed consent was also waived. Patients participating in the sub-study of collection of patient reported outcomes (PROs) were asked to provide individual written informed consent to participate and for linkage of their PRO data to provincial administrative data. The study was approved by the Ontario Cancer Research Ethics Board, a centralized ethics board used by 18 of the participating cancer centres (15-041), the

Sault Area Hospital Research Ethics Board, and the Rouge Valley Health System Research Ethics Board.

Intervention

The cluster randomization was performed at the Ontario Clinical Oncology Group (OCOG) in Hamilton, Ontario and used population-based administrative health data to determine historical patient volumes (forming strata of large, medium and small centres), number of acute care visits, Charlson comorbidity index, rurality, cancer stage, chemotherapy regimen, facility type, and center surveys to determine nursing model and proportion of non-English speaking patients. Centres randomized to the intervention arm were to offer the proactive telephone symptom management program to all eligible patients commencing adjuvant or neoadjuvant chemotherapy for early-stage breast cancer during the enrollment period.

Participants in the intervention arm received a copy of the Symptom Self-Management Booklet-Patient Edition and two structured follow-up calls during each chemotherapy cycle: between 24 to 72 hours and between 8 to 10 days after start of each cycle (**Supplementary Figure 1**). During the calls, symptoms were assessed by locally-designated oncology nurses using a standardized questionnaire, which addressed nine common chemotherapy-related toxicities: (1) nausea, (2) vomiting, (3) mouth and throat sores, (4) pain, (5) aching joints and aching muscles, (6) loose and watery stools, (7) shivering or shaking chills, (8) constipation, and (9) fatigue or tiredness. Standardized symptom management guidance was provided using the Symptom Self-Management Booklet - Healthcare Provider Edition and the Telephone Follow-up

Script. Additional unscheduled calls to follow-up on symptoms or to provide additional support were completed at the discretion of the care team.

Control

Participants in the control centres were to receive standard of care as per their institution. Typically, this involved baseline chemotherapy teaching and advice to call the cancer centre regarding treatment related symptoms or concerns between clinic visits.

Primary Outcome

The primary outcome was the cluster-level mean number of ED/H visits per patient during the at-risk period defined as the time on chemotherapy treatment starting with the first day of cycle 1 until 30 days following the last chemotherapy treatment. It was measured using Ontario administrative healthcare data. Ontario has a single-payer universal healthcare system with a comprehensive population-based cancer registry capturing diagnostic and demographic information on approximately 98% of incident cancer cases.[14] All patients with breast cancer at the participating centres who initiated adjuvant or neo-adjuvant chemotherapy during the intervention period were identified from the provincial Activity Level Reporting database which includes information on drugs received, dates of treatment and institution where treatment was given. The Ontario Cancer Registry was used to confirm the patient had early-stage breast cancer. The National Ambulatory Care Reporting System and Canadian Institutes for Health Information Discharge Abstract Database were utilized to obtain information on ED visits and hospitalizations, respectively; details of this methodology have been described previously.[1.] Briefly, all unique ED visits and hospitalizations during the at-risk period were identified and

added for each patient. ED visits that led to a hospitalization were counted as a single acute care episode.

Secondary Outcomes

Implementation fidelity was assessed based on the core elements specified by Carrol et al.[15] Adherence was defined as completion of 80% of the expected toxicity management calls (patient reached and counseling provided) within the protocol-specified call window. Penetration was defined as the proportion of patients who received the intervention at the 10 intervention sites out of those eligible, which was determined from administrative health data.

A PRO sub-study of approximately 25 consecutive, consenting patients enrolled at each participating centre completed validated questionnaires. Participants completed the PRO questionnaires prior to the start of the first (Visit 1; baseline) and second cycles of chemotherapy (Visit 2), and within 60 days of the end of treatment (Visit 3). Participants receiving a chemotherapy regimen where they switch to a different drug part way through (usually addition of a taxane), completed an additional PRO questionnaire prior to the start of the second cycle of the second drug (Visit 2a). Severity of treatment toxicities was measured using the National Cancer Institute PRO version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE)[16-17] self-report tool. Self-efficacy or confidence in managing symptoms was measured using the Stanford Self-Management Self-Efficacy Scale,[18] and general quality of life by the EQ-5D-3L.[19] The Patient Health Questionnaire (PHQ)[20] and Generalized Anxiety Disorder (GAD)[21] scales measured major depression and anxiety, respectively. Physical, social and family wellbeing were measured using the Functional Assessment of Cancer Therapy-

Breast (FACT-B) scale.[22] Coordination and continuity of care was evaluated using the adapted Picker survey;[23-24] self-care during chemotherapy was evaluated using the Leuven questionnaire (L-PaSC).[25]

Statistical Analysis

A detailed sample size calculation has been published previously.[12] Briefly, we applied two different simulation approaches to historical administrative health data from Ontario to estimate the sample size for the cRCT; both approaches resulted in similar estimates. With approximately 73 women per centre (total sample size=1460) from 20 centres, we would achieve 80% power to detect a 33% reduction in the number of ED/H visits, with a one-sided alpha of 2.5%. For the PRO sub-study, at least 25 participants per centre (total sample size: 500) needed to be enrolled for 80% power (one-sided alpha 2.5%) to detect a treatment effect size of 0.35 standard deviations.

Demographic and clinical characteristics of full and PRO sub-study cohorts were summarized using descriptive statistics. Impact of the intervention on the unweighted centre-level mean number of ED/H per patient was calculated at both the stratum size-level and overall, for both the intervention and control arms, and compared using t-scores (evaluated using only the 2,890 acceptable permutations of the 20 centres) and the randomization test. Impact of penetration of the intervention on the primary outcome was evaluated using negative binomial regression. PRO secondary outcomes were measured at the patient level. The worst grade of treatment-related toxicities from the NCI PRO-CTCAE was summarized for the intervention and control arms and compared using Fisher's exact two-sided test. PROs

were evaluated using linear mixed models for repeated measures (fixed effects include the baseline QoL score, intervention, visit, intervention-by-visit interaction, and size stratum; random effects are centres, with an unstructured covariance matrix for visits and the clustering of the individuals within centres). All analyses were conducted using SAS 9.4 and R 3.5 on the Institute for Clinical Evaluative Sciences (ICES) Data and Analytic Virtual Environment secure server.

Patient and Public Involvement

Patient partners at Cancer Care Ontario provided informal feedback on the study concept. Patients or the public were not formally involved in the design, evaluation or dissemination of this study.

RESULTS

Cohort Description

During the enrollment period from February 2016 to November 2017, 2158 patients initiated adjuvant or neoadjuvant chemotherapy for early stage breast cancer at the 20 participating institutions (**Figure 1**). Baseline characteristics (**Table 1**) were similar in the intervention (n=944) and control arms (n=1214). The median age was 55 and the majority of participants had stage 2 disease. The most commonly used regimens were AC-paclitaxel and FEC-docetaxel. Five hundred and eighty patients participated in the PRO sub-study.

Intervention Delivery Characteristics

The number of participants who received the intervention varied by cancer centre (range=44-141 patients). The overall intervention penetration at centres randomized to the intervention arm was 68.2% (centre-level range=50-86%). Of the 7,940 expected proactive calls, 78% were completed (centre-level range=60-95%), of which 84% were completed within the time window (centre-level range=68-97%). No trend was observed between centre size and the proportion of calls delivered; 347 unscheduled, additional calls were made at the discretion of the intervention nurses over the course of delivering the intervention; the number of additional calls completed varied by cancer centre (range=1-115 calls).

Impact of Intervention on Emergency Department Visits and/or Hospitalizations

Overall, 47% of patients had at least one ED/H visit during treatment. No statistically significant difference was observed in the centre-level mean number of ED/H per patient between the intervention (0.91; standard deviation [SD]=0.28) and control arms (0.94; SD=0.40; p=0.85; **Table 2**). Additionally, there were no cluster-level differences between intervention and control arms for ED visits alone (mean absolute difference= -0.010; 95% confidence interval [CI], -0.216 to 0.145; p=0.92), or hospitalizations alone (mean absolute difference= -0.014; 95% CI, -0.064 to 0.035; p=0.67). Penetration of the intervention had little impact on the number of ED/H visits in large and medium-sized centres; however, for the small centres, the number of ED/H visits decreased by 25% for each percentage point increase in penetration (p<0.001; **Supplementary Table 1**).

Impact on Patient-Reported Outcomes

There were fewer patients with grade 3 toxicities in the intervention arm (48% vs 58%, p=0.028; **Table 3**). Significant differences were observed between the intervention and control arms in the proportion of patients experiencing grade 3 fatigue (21% vs 30%), aching joints (22% vs 30%), and aching muscles (19% vs 27%). No significant effect of the intervention on anxiety (GAD; p=0.59) or depression (PHQ; p=0.07) was observed (**Table 4**). Additionally, no improvement in self-efficacy (Stanford; p=0.57), or coordination of care (Picker; p=0.67) was observed in patients receiving the intervention. Over the at-risk period, patients in the intervention group demonstrated a smaller decline from baseline for FACT Trial Outcome Index (-6.1 vs -9.0; difference=2.9, 95% CI, 0.8 to 5.0; p=0.008) and FACT Physical Well-being (-3.0 vs -4.6, difference=1.6, 95% CI, 0.7 to 2.5; p<0.001) **(Table 4)**

DISCUSSION

Over the last decade, there has been substantial interest in identifying effective approaches to support patients with cancer remotely during chemotherapy to minimize toxicity, improve quality of life, and decrease acute care utilization. In our trial, we found that despite high overall utilization rate of acute care in this patient population (47% of patients had at least one emergency department visit or hospitalization during treatment), proactive telephone toxicity management during curative intent chemotherapy did not lead to a decrease in rates of ED/H between intervention and control centres. The failure to detect a difference could potentially be due to low penetration (overall 68.2%; range=50-86%) and/or low intervention fidelity in some centres (78% of calls were completed; centre-level range=60-95%),

diluting any potential observable effect, albeit we did not see a strong correlation between penetration and ED/H, except for small centres. Unfortunately, it is not unusual for complex interventions that demonstrate early promise to fail to translate to appreciable differences in outcomes upon large-scale implementation.[26] Furthermore, proactive support may have directed patients to ED who would otherwise not have sought care as some of the nursing algorithms advise patients to seek care in the ED if no other avenues for urgent evaluation are available which was the case for most participating centres during the course of the study. Additionally, lack of effect could be due to temporal changes in supportive care during cancer treatment across Ontario during the study period as enhancing toxicity management for patients with cancer on systemic treatment was a provincial priority.[27-29] As a result, some of the control centres may have introduced interventions in their centres to improve patient support during therapy such establishment of urgent care clinics.[30]

Comparison with Other Studies

Our intervention was shown to be associated with a lower proportion of patients with grade 3 toxicities, especially fatigue, aching joints and aching muscles, as well as some statistically significant findings in QoL outcomes that did not fully meet criteria for a clinically important difference.[31] These findings are in keeping with previous studies, which have shown that proactive remote symptom monitoring during cancer treatment is associated with a positive impact on symptoms and QoL[-8, 32-33] and suggests that impact on symptom burden may be scalable beyond individually randomized trials. In contrast to physical symptoms, our intervention was not associated with improvements in other PROs such as self-efficacy, anxiety or depression. Lack of effect on self-efficacy may be due to high baseline scores and a possible

ceiling effect, and a focus on symptom management as opposed to coaching application of self-management behaviours. A recent single centre trial of remote electronic monitoring coupled with self-management coaching during chemotherapy reported improvement in self-efficacy in the intervention arm.[33] Lack of impact on anxiety or depression may be due to the content of the calls, which focused on physical rather than emotional symptoms.

Strengths and Limitations

There are a number of unique design aspects to our study including the cluster randomization, introduction of the intervention as a process improvement change at the level of each intervention centre, a pragmatic approach which mimics implementation in routine practice, and the use of existing population-based administrative health data to evaluate the primary outcome. There has been substantial interest in leveraging routinely collected health data to augment clinical trials to both decrease cost and burden[26], albeit a recent systematic review suggests that such trials may show smaller treatment effects than traditional trials.[34] Our study demonstrates the feasibility of utilizing routinely collected administrative data to evaluate trial outcomes. Utilization of administrative data in our study facilitated the recruitment of smaller, community centres into our trial for whom extensive primary data collection may have been a barrier to participation. Furthermore, for outcomes such as healthcare utilization, administrative data may be more accurate than patient self-report.

These are some limitations to this study that warrant consideration such as lag in data reporting which can increase time to analysis, and the lack of clinical contextual information required to understand appropriateness of care or potential drivers of observed outcomes,

such as patient preferences or unmeasured confounders.[35] Additionally, the study was conducted in Ontario, Canada which has a universal, single-payer system so administrative records capture the complete care episode for patients with cancer consistently and completely.[36] There may be issues with operationalizing a similar methodology in multi-payer systems.

Conclusions

In summary, remote proactive telephone-based toxicity management during chemotherapy did not lead to fewer ED/H in this multi-centre cluster RCT but was associated with fewer grade 3 toxicities and a smaller decline in QoL. Given the observed improvement in PROs and the high-level of acceptability of the intervention by both patients[11] and providers[37], together with growing body of evidence from other studies showing benefits of remote monitoring during chemotherapy,[7-8,32-33] future evaluations of proactive remote management should focus on pragmatic large-scale implementation in routine care settings. While implementation issues with large-scale program evaluations persist, with the rapid rise in remote care due to the novel coronavirus pandemic, identification of scalable strategies for remote support of patients during cancer treatment is particularly relevant, including telephone based interventions as this remains a key method for virtual care delivery.[38] In view of resource implications of large-scale implementation of such programs, provision of proactive monitoring during cancer treatment to high-risk patients (those receiving certain regimens), or high-risk situations (at the beginning of chemotherapy or in advanced disease)[7,39] may facilitate wide spread adoption and should be prioritized for study.

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Competing Interests: Authors CCE and EG hold appointments at the Ontario Institute for Cancer Research (OICR) Health Services Research Program. All authors declare no other relationships or activities that could appear to have influenced the submitted work.

Previous Presentation: Findings were presented virtually at the European Society for Medical Oncology (EMSO) annual congress in September 2020.

Data Access: Relevant anonymized patient level data available on reasonable request.

Dissemination to participants and related patient and public communities: There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Guarantor: The lead author (MKK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

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FIGURE LEGENDS:

Supplementary Figure 1. Study schema. Originally published in: BMC Cancer. 2019 Sep 5;19(1):884.

Figure 1: CONSORT diagram

Table 1. Demographic and clinical characteristics of full cohort and PRO sub-study

Characteristic	Full Cohort (N=2158)		PRO Sub-study (N=580)	
	Intervention n = 944	Control n = 1214	Intervention n = 283	Control n = 297
Age Group: *n (%)* †				
<40	86 (9)	99 (8)	31 (11)	25 (8)
40-44	84 (9)	99 (8)	26 (9)	22 (7)
45-49	117 (12)	173 (14)	42 (15)	47 (16)
50-54	171 (18)	212 (17)	44 (16)	62 (21)
55-59	128 (14)	209 (17)	38 (13)	56 (19)
60-64	135 (14)	170 (14)	45 (16)	42 (14)
65-69	117 (12)	128 (11)	39 (14)	25 (8)
70-74	61 (6)	74 (6)	12 (5)	12 (4)
≥ 75	45 (5)	50 (4)	6 (2)	6 (2)
Stage: *n (%)*				
I	215 (23)	232 (20)	63 (22)	61 (21)
II A	264 (28)	334 (28)	82 (29)	90 (30)
II B	216 (23)	299 (25)	67 (24)	68 (23)
III A	139 (15)	215 (18)	44 (16)	57 (19)
III B	44 (5)	57 (5)	9 (3)	8 (3)
III C	42 (4)	51 (4)	9 (3)	7 (2)
IV	<6 (NR)	<6 (NR)	<6 (NR)	<6 (NR)
unknown	22 (2)	23 (2)	<6 (NR)	<6 (NR)
Chemotherapy Details:				
Regimen: *n (%)*				
AC-P	417 (44)	539 (44)	118 (42)	139 (47)
FEC-D	234 (25)	331 (27)	80 (28)	86 (29)
TC	201 (21)	182 (15)	58 (20)	46 (15)
AC-Doc	8 (1)	36 (3)	<6 (NR)	<6 (NR)
Other	84 (9)	126 (10)	25 (9)	23 (8)
Class*: *n (%)*				
Anthracycline	664 (70)	945 (78)	202 (71)	234 (79)
Docetaxel	478 (51)	575 (47)	156 (55)	141 (47)
Paclitaxel	456 (48)	583 (48)	124 (44)	149 (50)
Charlson Score: *n (%)*				
0	226 (24)	336 (28)	60 (21)	74 (25)
1	35 (4)	54 (4)	10 (4)	7 (2)
≥ 2	20 (2)	14 (1)	<6 (NR)	<6 (NR)
unknown	663 (70)	810 (67)	209 (74)	213 (72)

Characteristic	Full Cohort (N=2158)		PRO Sub-study (N=580)	
	Intervention n = 944	Control n = 1214	Intervention n = 283	Control n = 297
Income Quintile: *n (%)*				
1	148 (16)	180 (15)	40 (14)	34 (11)
2	184 (19)	215 (18)	54 (19)	40 (14)
3	191 (20)	255 (21)	58 (20)	55 (19)
4	186 (20)	268 (22)	61 (22)	85 (29)
5	234 (25)	292 (24)	70 (25)	80 (27)
ADG Total: *n (%)*				
0 - 4	171 (18)	211 (18)	50 (18)	60 (20)
5 - 9	527 (56)	682 (56)	160 (56)	172 (58)
≥ 10	246 (26)	321 (26)	73 (26)	65 (22)
mean (range)	7.6 (0, 20)	7.5 (0, 25)	7.6 (1, 20)	7.1 (0, 23)
Rural: *n (%)*				
Yes	79 (8)	116 (9)	27 (10)	34 (11)
No	864 (92)	1094 (90)	256 (90)	260 (88)

† median age is 55.7 (estimated from grouped data)
* patients may fit into more than one category

PRO=patient-reported outcomes; AC-P=adriamycin, cyclophosphamide, paclitaxel; FEC-D=fluorouracil, epirubicin, cyclophosphamide, docetaxel; TC=docetaxel, cyclophosphamide; AC-Doc=adriamycin, cyclophosphamide, docetaxel; ADG=adjusted diagnostic group

Table 2. Unweighted centre-level mean number of ED/H visits/person by centre size during the at-risk period

Stratum Size	Intervention		Control		Int – Ctl Difference
	N (k)	*mean (SD)*	*N (k)*	*mean (SD)*	*mean (95% CI)*
Large	532 (5)	0.90 (0.07)	778 (5)	0.74 (0.17)	0.17 (-0.05 to 0.38)
Medium	302 (3)	0.92 (0.23)	216 (2)	0.97 (0.16)	-0.04 (-0.60 to 0.51)
Small	110 (2)	0.92 (0.76)	220 (3)	1.25 (0.63)	-0.33 (-3.25 to 2.58)
Overall	**944 (10)**	**0.91 (0.28)**	**1214 (10)**	**0.94 (0.40)**	**-0.024 (-0.24 to 0.15)***

ED/H=emergency department visit or hospitalization; N=number of patients; k=number of centres; SD=standard deviation; CI=confidence interval; Int=Intervention; Ctl=Control; at-risk period=start to end of chemotherapy + 30 days

* Overall group comparison unadjusted p=0.85 (when adjusted for size strata p=0.94) based on randomization test

Table 3. Summary of worst grade chemotherapy toxicity post-baseline by group and toxicity type

Toxicity Type	Patients with Grade 3 Toxicity n (% of Group)		
	Intervention (n=278)	**Control** (n=283)	*P-value**
Fatigue, tiredness or lack of energy	58 (21)	90 (32)	**0.004**
Loose and watery stools, diarrhea	11 (4)	<6 (NR)	0.99
Nausea	23 (8)	24 (8)	0.99
Vomiting	<6 (NR)	<6 (NR)	0.99
Pain	85 (31)	100 (35)	0.24
Aching joints	61 (22)	84 (30)	0.043
Aching muscles	53 (19)	77 (27)	0.028
Constipation	26 (9)	39 (14)	0.11
Mouth and throat sores	11 (4)	12 (4)	0.99
Shivering or shaking chills	6 (2)	10 (4)	0.45
Any toxicity	134 (48)	163 (58)	0.028

NR=not reported because counts < 6 (Institute for Clinical Evaluative Sciences where analyses were performed does not allow reporting of cells with less than 6 patients)

* Fisher's exact two-sided test

Table 4. Patient Reported Outcomes: Linear mixed model analysis for the change from baseline (V1)

Scale	Visit Change	Intervention Estimate (SE)	Control Estimate (SE)	Int - Ctl Difference† Estimate (95% CI)	*P-value*	Overall Effect* *(P-value)*	
						Visit	**Intervention**
Functional Assessment for Cancer Therapy for Patients with Breast Cancer (FACT-B)							
Trial Outcome Index	V2–V1	-2.4 (0.7)	-4.9 (0.6)	2.5 (0.7 to 4.3)	**0.007**	**<0.001**	**0.004**
	V2a–V1	-7.7 (0.8)	-9.6 (0.8)	2.0 (-0.2 to 4.2)	0.08		
	V3–V1	-6.1 (0.8)	-9.0 (0.8)	2.9 (0.8 to 5.0)	**0.008**		
Physical Well-being	V2–V1	-2.4 (0.3)	-3.4 (0.3)	1.0 (0.2 to 1.9)	0.022	**<0.001**	**0.001**
	V2a–V1	-4.3 (0.4)	-5.3 (0.3)	1.0 (0.0 to 2.0)	0.045		
	V3–V1	-3.0 (0.3)	-4.6 (0.3)	1.6 (0.7 to 2.5)	**0.0003**		
Social Well-being	V2–V1	0.0 (0.2)	-0.3 (0.2)	0.3 (-0.3 to 0.9)	0.32	**<0.001**	0.51
	V2a–V1	-0.5 (0.3)	-0.6 (0.2)	0.1 (-0.6 to 0.8)	0.73		
	V3–V1	-0.8 (0.2)	-0.9 (0.2)	0.1 (-0.6 to 0.8)	0.78		
Emotional Well-being	V2–V1	1.4 (0.2)	1.4 (0.2)	0.0 (-0.4 to 0.4)	0.99	0.95	0.89
	V2a–V1	1.2 (0.2)	1.6 (0.2)	-0.3 (-0.9 to 0.2)	0.21		
	V3–V1	1.6 (0.2)	1.3 (0.2)	0.3 (-0.2 to 0.8)	0.30		
Functional Well-being	V2–V1	-0.6 (0.3)	-1.5 (0.3)	0.8 (0.1 to 1.6)	0.029	**<0.001**	0.15
	V2a–V1	-2.8 (0.3)	-2.9 (0.3)	0.1 (-0.8 to 1.0)	0.82		
	V3–V1	-2.0 (0.3)	-2.5 (0.3)	0.5 (-0.3 to 1.4)	0.21		
EuroQol (EQ-5D-3L)							
EQ Index	V2–V1	0.01 (0.01)	0.03 (0.01)	-0.02 (-0.04 to 0.00)	0.08	**<0.001**	0.52
	V2a–V1	0.01 (0.01)	-0.02 (0.01)	0.02 (-0.01 to 0.05)	0.13		
	V3–V1	-0.03 (0.01)	-0.04 (0.01)	0.01 (-0.01 to 0.04)	0.23		
EQ VAS	V2–V1	1.3 (0.8)	-0.8 (0.8)	2.1 (-0.1 to 4.2)	0.06	**<0.001**	0.031
	V2a–V1	-2.4 (1.1)	-5.8 (1.1)	3.4 (0.4 to 6.4)	0.029		
	V3–V1	-3.6 (1.0)	-4.7 (1.0)	1.1 (-1.6 to 3.8)	0.42		
Stanford Self-Efficacy							
Stanford	V2–V1	0.3 (0.1)	0.3 (0.1)	0.0 (-0.3 to 0.3)	0.95	**0.009**	0.57
	V2a–V1	0.2 (0.1)	-0.1 (0.1)	0.2 (-0.1 to 0.6)	0.20		
	V3–V1	0.3 (0.1)	0.3 (0.1)	0.0 (-0.3 to 0.3)	0.93		
Adapted Picker Survey							
Picker	V2–V1	6.0 (1.4)	4.0 (1.4)	2.0 (-2.0 to 5.9)	0.33	0.093	0.67
	V2a–V1	7.0 (1.8)	7.1 (1.7)	-0.1 (-5.1 to 4.9)	0.97		
	V3–V1	4.6 (1.6)	4.2 (1.5)	0.4 (-3.9 to 4.7)	0.85		
Generalized Anxiety Disorder							
GAD	V2–V1	-2.1 (0.2)	-2.1 (0.2)	0.0 (-0.5 to 0.6)	0.93	0.91	0.59
	V2a–V1	-2.4 (0.2)	-2.0 (0.2)	-0.5 (-1.2 to 0.2)	0.16		
	V3–V1	-2.1 (0.2)	-2.2 (0.2)	0.1 (-0.6 to 0.7)	0.87		
Patient Health Questionnaire							
PHQ	V2–V1	0.3 (0.2)	0.7 (0.2)	-0.4 (-1.0 to 0.2)	0.16	**<0.001**	0.07
	V2a–V1	1.2 (0.3)	1.7 (0.3)	-0.5 (-1.2 to 0.3)	0.22		
	V3–V1	0.6 (0.2)	1.0 (0.2)	-0.5 (-1.1 to 0.2)	0.14		

SE=standard error; CI=confidence interval; Int=Intervention; Ctl=Control; V1=baseline; V2=prior to start of second cycle; V2a=prior to start of second cycle of taxane (if they switched regimens); V3=within 60 days of the end of chemotherapy; VAS=visual analog scale

† estimates of positive differences for FACT, EuroQol, Stanford and Picker scales, and negative differences for GAD and PHQ, suggest less decline for patients at the Intervention centres

* linear mixed models included visit, intervention and visit x intervention terms; no interaction terms were found to be statistically significant ($p<0.05$)

Figure 1.

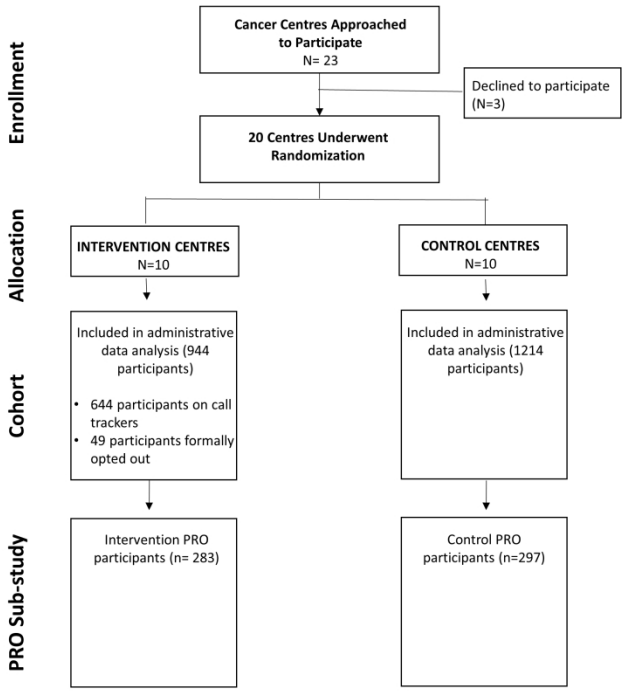
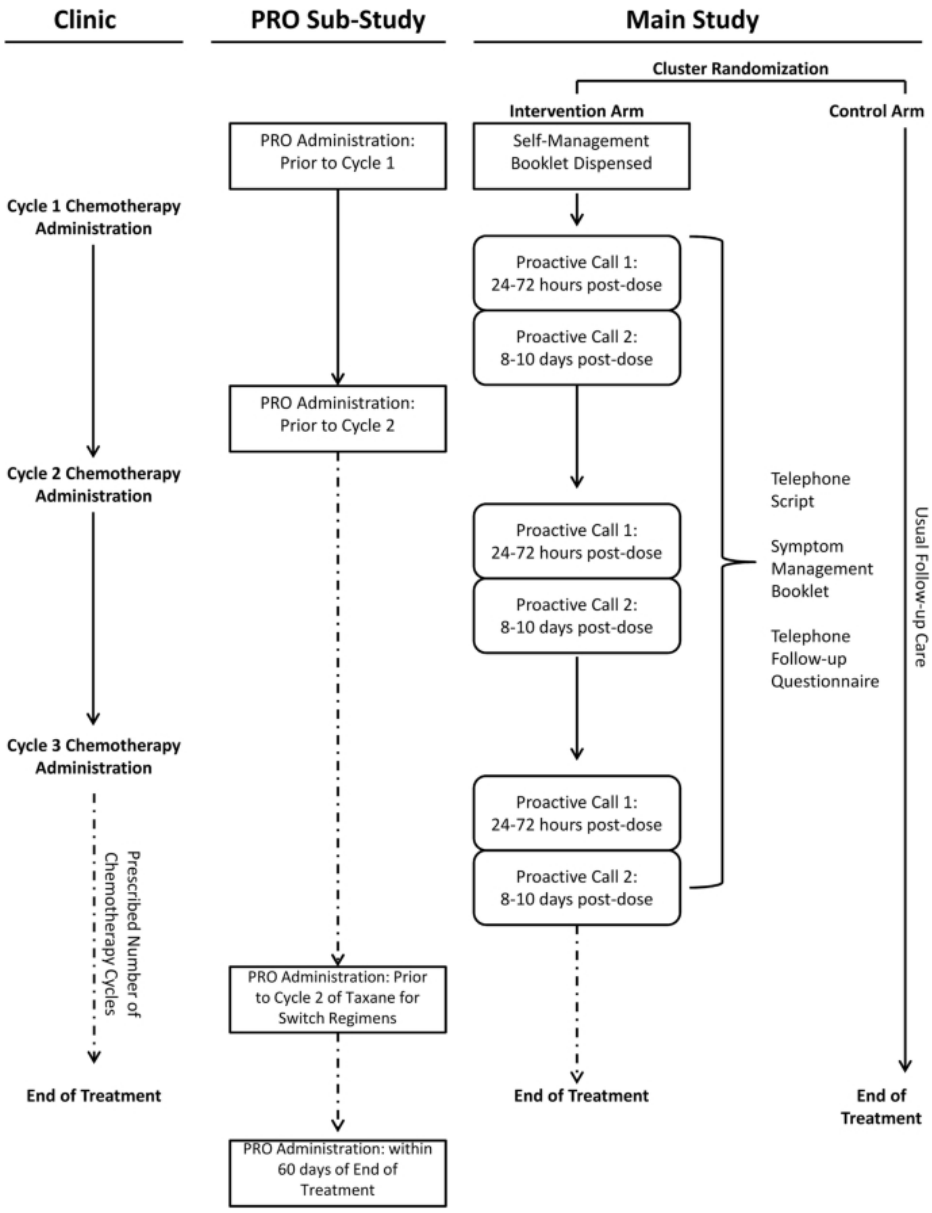


Figure 1: CONSORT diagram


Clinic
PRO Sub-Study
Main Study
Cluster Randomization
Intervention Arm
Control Arm
PRO Administration: Prior to Cycle 1
Self-Management Booklet Dispensed
Cycle 1 Chemotherapy Administration
Proactive Call 1: 24-72 hours post-dose
Proactive Call 2: 8-10 days post-dose
PRO Administration: Prior to Cycle 2
Cycle 2 Chemotherapy Administration
Telephone Script
Symptom Management Booklet
Telephone Follow-up Questionnaire
Usual Follow-up Care
Proactive Call 1: 24-72 hours post-dose
Proactive Call 2: 8-10 days post-dose
Cycle 3 Chemotherapy Administration
Proactive Call 1: 24-72 hours post-dose
Proactive Call 2: 8-10 days post-dose
Prescribed Number of Chemotherapy Cycles
PRO Administration: Prior to Cycle 2 of Taxane for Switch Regimens
End of Treatment
End of Treatment
End of Treatment
PRO Administration: within 60 days of End of Treatment

Supplementary Table 1. Association of Penetration with Primary Outcome in 10 Intervention Centres (n=944)

Toxicity Window	Centre Size	Primary Outcome		
		IRR* *Estimate (95% CI)*	**% Change** *Estimate (95% CI)*	*P-value*
30 Days	**Large**	1.000 (0.993 to 1.007)	0.0 (-0.7 to 0.7)	0.95
	Medium	1.009 (0.999 to 1.020)	0.9 (-0.1 to 2.0)	0.09
	Small	0.746 (0.660 to 0.844)	-25 (-34 to -15)	**<0.001**
60 Days	**Large**	1.000 (0.993 to 1.007)	0.0 (-0.7 to 0.7)	0.95
	Medium	1.009 (0.998 to 1.019)	0.9 (-0.2 to 1.9)	0.10
	Small	0.749 (0.664 to 0.845)	-25 (-34 to -16)	**<0.001**
90 Days	**Large**	1.000 (0.992 to 1.006)	-0.0 (-0.8 to 0.6)	0.83
	Medium	1.009 (0.998 to 1.019)	0.9 (-0.2 to 1.9)	0.10
	Small	0.729 (0.648 to 0.820)	-27 (-35 to -18)	**<0.001**