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ORIGINAL ARTICLE

Feasibility of using a pragmatic trials model to compare two primary febrile neutropenia prophylaxis regimens (ciprofloxacin versus G-CSF) in patients receiving docetaxel-cyclophosphamide chemotherapy for breast cancer (REaCT-TC)

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Abstract

Purpose Optimal primary febrile neutropenia (FN) prophylaxis (i.e. ciprofloxacin or granulocyte-colony stimulating factors [G-CSF]) for patients receiving docetaxel-cyclophosphamide (TC) chemotherapy is unknown. We assessed the feasibility of using a novel pragmatic comparative effectiveness trial to compare these standard-of-care options.

Methods Early-stage breast cancer patients receiving TC chemotherapy were randomised to either ciprofloxacin or G-CSF. Trial methodology consists of broad eligibility criteria, simply-defined endpoints, integrated consent model incorporating oral consent, and web-based randomisation in the clinic. Primary feasibility endpoints included patient and physician engagement (if > 50% of patients approached agree to participate and if > 50% of physicians approached patients for the study). Secondary clinical endpoints included the following: first occurrence rates of FN, treatment-related hospitalisation, or chemotherapy dose reduction/delay/discontinuation, as well as patient satisfaction with the oral consent process.

Results Of 204 patients approached, 91.2% (186/204) agreed to randomisation. Sixteen of twenty (80%) participating medical oncologists randomised patients. Median patient age was 57.7 (range 31.8–84.1). The 186 patients received 557 cycles of chemotherapy. Overall incidences of first events by patient ($n = 186$) were as follows: FN (18/186, 21.43%), treatment-related hospitalisation (11/186, 13.10%), chemotherapy reduction (19/186, 22.62%), chemotherapy discontinuation (16/186, 19.05%), and chemotherapy delays (5/186, 5.95%). A total of 37.77% (69/186) of patients and 12.39% (69/557) of chemotherapy cycles had at least one of these first events. Patients were highly satisfied with the oral consent process.

Conclusion This study met its feasibility endpoints. This model offers a means of comparing standard-of-care treatments in a practical and cost-efficient manner.

Trial registration Trial registration: ClinicalTrials.gov: NCT02173262

Keywords Integrated consent model · Breast cancer · Febrile neutropenia · Filgrastim · Ciprofloxacin

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Introduction

Adjuvant docetaxel-cyclophosphamide (TC) chemotherapy is commonly used in patients with early-stage breast cancer [1]. Due to the risk of neutropenia and its associated consequences (including febrile neutropenia [FN], treatment-related hospitalisations, chemotherapy delays, dose reductions, and discontinuation), many treatment guidelines recommend that TC chemotherapy be co-administered with primary FN prophylaxis [2–4]. The choice of primary FN prophylaxis is usually either an antibiotic (e.g. ciprofloxacin) or granulocyte-colony stimulating factor (G-CSF) (e.g. filgrastim or pegfilgrastim) [1, 5]. However, despite extensive use of TC for over a decade and the significant differences in toxicity profile, route of administration, and cost between the two primary FN prophylaxis regimens, no trial has directly compared ciprofloxacin with G-CSF [6]. Hence, clinical equipoise about which agent to use exists [7].

Performing such a trial using a traditional clinical trial model would be challenging as it is unlikely that standard sources of funding (i.e. pharmaceutical funding) could be leveraged for a trial that would compare two funded standard-of-care treatment options. Our team has been evaluating trial models for comparisons of standard-of-care interventions that are more pragmatic, inexpensive, and practical [8, 9]. In the current study, we assessed the feasibility of performing a pragmatic, multi-centre randomised clinical trial using this novel trial methodology for comparing ciprofloxacin with growth factors (e.g. filgrastim, pegfilgrastim) as primary FN prophylaxis in patients receiving TC chemotherapy for early-stage breast cancer. If feasibility was demonstrated, then the study would be expanded in sample size to allow for a comparison of FN rates between ciprofloxacin and G-CSF.

Methods

Study population

Patients with newly diagnosed early-stage breast cancer who were seen at either the Ottawa Hospital Cancer Centre (Ottawa, ON), The Irving Greenburg Family Cancer Centre (Ottawa, ON) or the Cross Cancer Institute (Edmonton, AB) and who would receive TC chemotherapy with either ciprofloxacin or growth factors as primary FN prophylaxis were eligible. Eligible patients are as follows: had histologically confirmed primary breast cancer, have received no prior chemotherapy, planned to receive four cycles of TC chemotherapy, ≥ 19 years of age, able to provide verbal consent, and willing to complete a patient satisfaction survey at the end of the study. Exclusion criteria included a contraindication to either ciprofloxacin or G-CSF. The study was approved by the local Research Ethics Board at each participating centre (The Ottawa Health Science Network Research Ethics Board and Health Research Ethics Board of Alberta) and was registered on clinicaltrials.gov (NCT02173262) [10].

The rethinking clinical trials program

The development of the rethinking clinical trials (REaCT) program for comparing standard-of-care interventions is outlined elsewhere [8]. The key components include the following: selection of clinically relevant and practical questions; demonstration of clinical equipoise through surveys of knowledge users and completion of systematic reviews; simply-defined study endpoints and avoidance of superfluous data collection; use of an integrated consent model (ICM) incorporating oral consent [8, 9, 11]; efficient REB approval [12]; web-based randomisation in the clinic; and the use of real-time electronic data capture. While the current study methodology incorporated many of these processes, we also needed to demonstrate whether such a methodology was feasible for a real-world, multi-centre trial.

Trial design

Intervention Patients were randomised to either ciprofloxacin (500-mg PO BID for 7–14 days starting 5 days after chemotherapy) or G-CSF (as this was a comparison of standard-of-care options of patients with their physicians that could choose the type, dose, and duration of G-CSF use).

Consent process Potentially eligible patients were informed about the risks of FN with TC chemotherapy and the two different standard-of-care prophylactic treatments available to them. This integrated consent model is akin to a typical conversation between the physician and patient. The physician would give the patient a consent template that briefly outlines the study (Appendix 1) and explain both the idea of randomisation and the patient's right to decline study entry. After the patient's questions were answered, if the patient was eligible and willing to enter the study, this clinical interaction was documented in the patient's electronic health record. There was no written consent form and a clinical research associate did not perform the consent process.

Randomisation Eligible and consented patients were randomised either by the physician in the clinic or by a research associate using a web-based program. Randomisation was performed using a permeated block design.

Data collection Endpoint data was collected either from automatic emails sent to the treating physician when the patient was expected back in the clinic or from the patient's electronic medical record (EMR).

Outcomes

Primary outcomes

A combination of outcomes was collected to reflect the feasibility of performing a study with our innovative methods. These included the following: physician engagement (the proportion of physicians who agreed at study commencement to participate in the study and who did indeed approach patients for the study), patient engagement (the percentage of eligible patients approached who agreed to participate in the trial), accrual rates (the percentage of patients who received TC chemotherapy at the two Ottawa sites compared to the number of participants who agree to randomisation during the study period), patient/physician compliance (the percentage of patients or physicians who after randomisation declined the assigned treatment), and time to REB approval at each site. Patient satisfaction was collected after completion of chemotherapy using a formal satisfaction survey (Appendix 2).

Secondary outcomes

Secondary outcomes included clinical endpoint data such as rates of documented FN (defined as an absolute neutrophil count $< 0.5 \times 10^9$/L with oral temperature > 38.5 °C or two consecutive readings > 38.0 °C for 2 h [13]), treatment-related hospital admissions (and reasons), and the percentage of patients who required dose delays, dose reductions, or discontinuations. Documented *Clostridium difficile* infections during chemotherapy were also collected. This data was collected as the event that occurred first. For example, if a patient had FN and then a dose reduction, FN was the first event and the only event reported [9].

Sample size and statistical analysis

The a priori criteria that needed to be met to deem this feasibility trial successful were if > 50% of physicians who agree at study commencement to participate in the study do indeed approach patients for the study and if > 50% of appropriate patients approached agreed to participate in the randomised trial. There was no pre-defined sample size but was pragmatically defined as being reached once, all three cancer centres were enrolling patients and had at least one patient complete all four cycles of TC chemotherapy. Study results will be presented in aggregate (i.e. not by trial arm) and descriptively.

Results

Patient enrolment and baseline characteristics

The feasibility trial ran from September 18, 2014 to November 2, 2016. Data is available for 186 randomised patients over 557 cycles of TC chemotherapy. The baseline characteristics of the randomised patients are shown in Table 1. Median age (range) was 57.7 (31.8–84.1) and 22.5% (42/186) of patients were ≥ 65. The percentage of patients randomised to the ciprofloxacin or growth factor support was 93/186 (50%) and 93/186 (50%) respectively. For the patients randomised at the Ottawa Cancer Centre ($n = 70$), data was available on the types of growth factors prescribed. This was either filgrastim (67/70, 95.7%) or pegfilgrastim (3/70, 4.29%). With filgrastim, 93.8% of patients were prescribed 300-μg dose at either 5 (45.3%), 7 (20.3%), or 10 (32.8%) days with the first chemotherapy cycle (Table 1).

Primary outcome measures

Patient engagement

Of the 204 potentially eligible patients who were approached about the study, 186/204 (91.2%) agreed to randomisation. Reasons for declining the study ($n = 18$) are shown in Fig. 1.

Physician engagement

Sixteen of twenty physicians (80%) who initially agreed to participate in the study approached patients regarding the trial.

Accrual rates

Data was available for the number of patients starting chemotherapy for early-stage breast cancer during the study period compared with the number of patients actually entered on the study for the Ottawa site only. For the TC regimens, this percentage was 41.2% (142/345).

Patient/physician compliance with randomisation allocation

Patient adherence to treatment allocation was excellent. The percentage of participants who were randomised and received their allocated treatment was 185/186 (99.5%). The reason for not complying was because the patient decided not to proceed with chemotherapy. Physician compliance was 184/186 (98.9%) and the reasons were because the physicians chose not to proceed with chemotherapy ($n = 1$) and a change in prophylaxis treatment for a patient with a potential allergy to ciprofloxacin ($n = 1$).

Table 1 Baseline characteristics

	Total	Ciprofloxacin	Growth factor	*p*
N (%)	186	93 (50%)	93 (50%)	NA
Age (median)	57.75	56.43	58.52	0.2735
(range)	(31.82, 84.11)	(31.82, 80.63)	(35.81, 84.11)	
Age ≥ 65, *N* (%)	42 (22.58%)	19 (20.43%)	23 (24.73%)	0.483
Type of G-CSF[a]	–	–		
Pegfilgrastim	–	–	3 (4.29%)	
Filgrastim	–	–	67 (95.71%)	
Filgrastim dose				
300 μg			60 (93.8%)	
480 μg			2 (3.1%)	
Other			2 (3.1%)	
Duration of filgrastim				
5 days			29 (45.31%)	
7 days			13 (20.31%)	
10 days			21 (32.81%)	
Other			1 (1.56%)	
Start on study after randomisation	183 (98.39%)	91 (97.85%)	92 (98.92%)	1.0
Randomised patients that completed the study	102 (54.84%)	46 (49.46%)	56 (60.22%)	0.1406
Consented patients that completed the study	102 (55.74%)	46 (50.55%)	56 (60.87%)	0.1599

TC, docetaxel-cyclophosphamide

[a] This data was only available for patients at The Ottawa Hospital Cancer Centre

Secondary outcomes

Tables 2 and 3 summarise the results of the clinical endpoints. As this was a feasibility trial, data is not presented by study arm (i.e. ciprofloxacin versus G-CSF) as this would be methodologically incorrect.

Results by number of administered cycles of chemotherapy

The 186 patients received a total of 557 cycles of chemotherapy. Of the 186 patients in the study, 69/186 (37.08%) had a study-mandated first event endpoint (i.e. FN, treatment-related hospital admission (non-FN), chemotherapy dose delay/reduction, or discontinuation) and 102/186 (54.84%) completed four cycles of TC without an event (Table 2). Overall study-mandated first events were as follows: FN (18/69, 21.43%), treatment-related hospitalisation (11/69, 13.10%), chemotherapy dose reductions (19/69, 22.62%), discontinuations (16/69, 19.05%), and delays (5/69, 5.95%). Reasons for treatment-related hospitalisations ($n = 11$) were fever (3), cellulitis (2), appendicitis (1), renal toxicity (1), colitis (1), pneumonitis (1), cholangitis (1), and strep throat (1).

Other reasons for study discontinuation affected an additional 15 patients and included switch of prophylaxis treatment by physician (6 patients), infections (5 patients), skin rash (1 patient), prophylaxis treatment side effects (1 patient), patient non-compliance (1 patient), and issues with self-injection (1 patient).

Results by number of patients enrolled

The incidence of first events can also be presented as an aggregate of patients (i.e. 186) or of chemotherapy cycles (i.e. 557) in Table 3. Aggregate incidences of first events by patient ($n = 186$) are as follows: FN (18/186, 9.84%), treatment-related hospitalisation (11/186, 6.01%), chemotherapy dose reduction (19/186, 10.38%), chemotherapy discontinuation (16/186, 8.74%), and chemotherapy delays (5/186, 2.73%). *C. difficile* infections occurred in 2/186 (1.09%) patients, with both patients randomised to G-CSF. Aggregate incidences of first events by total number of chemotherapy cycles ($n = 557$) are as follows: FN (18/557, 3.23%) treatment-related hospitalisation (11/557, 1.97%), chemotherapy dose reduction (19/557, 3.41%), chemotherapy discontinuation (15/557, 2.87%), and chemotherapy delays (5/557, 0.9%). Overall, 37.7% (69/186) of patients and 12.39% (69/557) of chemotherapy cycles had one of these events as a first event.

Patient satisfaction survey

Patients were asked at their final study visit to complete a questionnaire evaluating their satisfaction with the study, its consent process, and the time commitments required for study participation (Appendix 2). Survey responses were received

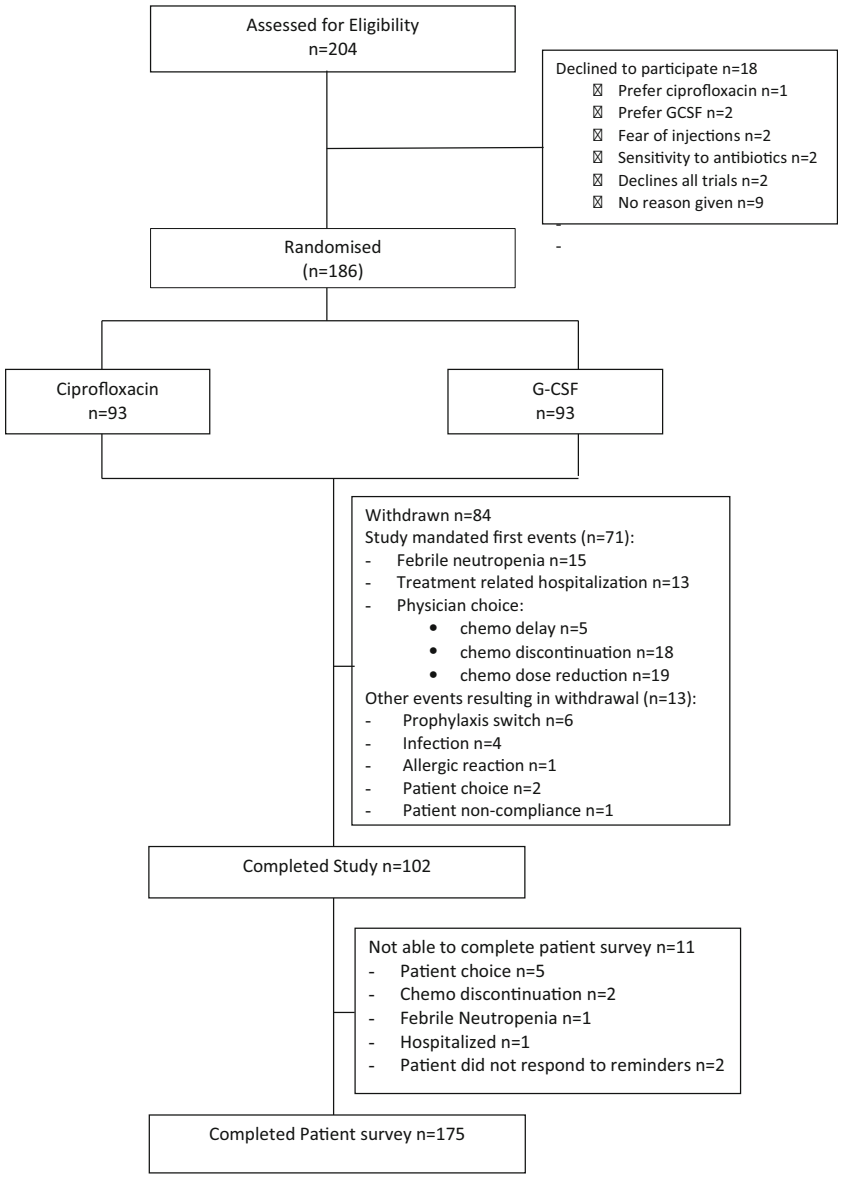

Fig. 1 Consort diagram

from 175/186 (94%) of participants (Table 4). The participants either "Agreed" or "Strongly Agreed" that the clinical trial was explained clearly to them by their oncologist (92%) and that their questions about the clinical trial were answered to their satisfaction (75%) while 15% stated they had no questions about the trial that required additional answers. Ninety-three percent of respondents said they would participate in this study again, if asked. In addition, participants either "Disagreed" or "Strongly Disagreed" that taking part in this study interfered with their quality of life (88%) or that they found taking part in this study was time-consuming (90%).

Table 2 Study-mandated first event endpoints (over all cycles)

First event $n = 69$	N (%)
Febrile neutropenia	18 (21.43%)
Treatment-related hospitalisation (non-FN)	11 (13.10%)
Chemo dose reduction	19 (22.62%)
Chemo discontinuation	16 (19.05%)
Chemotherapy delay	5 (5.95%)

Time for local or provincial research ethics approval

The regulatory aspects of opening a REaCT trial are outlined elsewhere [8]. The time from study submission to Ottawa Health Science Network Research Ethics Board (OHSN-REB) approval was 3 months. The Alberta Cross Cancer Centre REB approval was also 3 months after initial study submission to Health Research Ethics Board of Alberta (HREBA) following OHSN-REB approval.

Table 3 Clinical endpoint data reported by both the number of patients and the number of chemotherapy cycles administered

First study mandate event	*N*	Percentage by total number of patients (*n* = 186) (95%CI)	Percentage by total number of cycles (*n* = 557) (95% CI)
Febrile neutropenia	18	9.84 (5.93, 15.1)	3.23 (1.93, 5.06)
Treatment-related hospitalisation (non-FN)	11	6.01 (3.04, 10.5)	1.97 (0.99, 3.51)
Chemotherapy dose reduction	19	10.38 (6.37, 15.74)	3.41 (2.07, 5.28)
Chemotherapy discontinuation	16	8.74 (5.08, 13.81)	2.87 (1.65, 4.62)
Chemotherapy dose delay	5	2.73 (0.89, 6.26)	0.9 (0.29, 2.08)
Overall	69	37.7 (30.66, 45.15)	12.39 (9.77, 15.41)
Other events	15	8.2 (4.66, 13.16)	2.69 (1.51, 4.4)
C. difficile	2	1.09 (0.13, 3.89)	0.36 (0.04, 1.29)
Other infection[a]	6	3.28 (1.21, 7)	1.08 (0.4, 2.33)

[a] Infection excludes FN and *C. difficile* infections, but did not result in hospitalisation (e.g. viral infections and cellulitis)

Discussion

A recent systematic review of studies of patients receiving TC chemotherapy showed a FN rate of 27% in the absence of primary prophylaxis and this was reduced to 5% with primary FN prophylaxis [6]. Unfortunately, many of the studies in this review were retrospective and often did not include the type of primary FN prophylaxis given. Indeed, the original study leading to the approval of TC as an effective adjuvant chemotherapy regimen in breast cancer patients did not specify whether prophylaxis was used [1]. It was only in the subsequent publication when it was stated that the majority of patients received prophylactic ciprofloxacin [14]. It is clear that despite the widespread use of TC chemotherapy in patients with early-stage breast cancer and the known efficacy of FN prophylaxis, the optimal form of prophylaxis remains unknown [6–8].

This is problematic from both patient and health care system perspectives as there are considerable differences both in terms of toxicity and cost between these strategies. Growth factor support is expensive both in terms of direct (i.e. direct costs to the patient and/or the health care system) [15] and indirect (i.e. paying nursing staff to administer and/or to teach patients to self-administer subcutaneous injections) costs and may be associated with clinically important adverse effects (local and systemic pain). Ciprofloxacin, while relatively inexpensive, is associated with its own adverse effects. Identification of optimal primary FN prophylaxis regimen is an important clinical question. Thus, establishing the most effective regimen may offer not only cost savings, but also improve patient comfort and acceptability in a real-world setting [16].

In the current funding environment, while pragmatic trials are important to the health care system, it is unlikely that traditional funding sources (e.g. pharmaceutical company or government funding from peer-reviewed sources) will fund a trial comparing two standards of care and funded treatment options. For that reason, our group has been evaluating novel methodologies for comparing

Table 4 Patient satisfaction survey results

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Not applicable
The clinical trial was explained clearly to me by my oncologist.	2 (1.14%)	3 (1.71%)	9 (5.14%)	53 (30.29%)	108 (61.71%)	
I thought that the questions I had about the clinical trial were answered to my satisfaction.	1 (0.57%)	3 (1.71%)	12 (6.86%)	46 (26.29%)	86 (49.14%)	27 (15.43%)
If I was asked to participate in this study again, I would say yes.	1 (0.57%)		7 (4.0%)	52 (29.71%)	111 (63.43%)	4 (2.29%)
I found that taking part in this study interfered with my quality of life.	125 (71.43%)	30 (17.14%)	7 (4.0%)	5 (2.86%)	2 (1.14%)	6 (3.43%)
I found that it was time-consuming to take part in this study.	131 (74.86%)	27 (15.43%)	7 (4.0%)	1 (0.57%)	3 (1.71%)	6 (3.43%)

standard-of-care interventions in a pragmatic and relatively inexpensive manner. The major difference in our process compared to a typical clinical trial is the use of the oral consent integrated into care, which involves the physician having a conversation with the patient about the risks and benefits of potential interventions. This clinical interaction is then documented in the physician clinic note, as ordinarily done in practice, as a permanent record that the patient was fully informed about the study. The patient is also given a paper copy of the consent template. Web-based randomisation in the clinic by the physician (or designate) also means that the patient can expeditiously receive their allocated treatment by the end of the consultation. We therefore sought to evaluate whether the use of a novel trials methodology would be feasible to answer this important clinical question.

Feasibility was demonstrated with 91.2% (186/204) of appropriate patients approached agreeing to participate in the randomised trial, and 80% of physicians who agreed at study commencement to participate in the study actually approaching patients for the study. For a study using an innovative consent model, it was reassuring that REB approval was granted within 3 months, a timeframe that is consistent with more traditional trial methodologies. It is also important to acknowledge that the majority of participants, when surveyed, felt that the oral consent methodology was explained clearly to them by their oncologist. They agreed that their questions about the clinical trial were answered to their satisfaction and that, if asked, they would participate in this study again. In addition, participants did not feel the trial participation interfered with their quality of life or was time-consuming.

With respect to secondary endpoints, it was evident that TC is not an innocuous regimen, with 37.7% (69/186) of patients and 12.39% (69/557) of chemotherapy cycles experiencing one of the study-mandated first events (i.e. FN, treatment-related hospitalisation, chemotherapy dose reduction, discontinuation, or delay). The most common event was febrile neutropenia. It is challenging to compare these rates with other trials and publications as trial data is often incomplete with respect to reporting the incidence of important events. For example, a trial may report FN rates but not hospitalisations for other reasons, giving a false impression of the toxicity of a regimen in real-world practice [1]. We therefore presented our results as aggregates of all patients and also of all chemotherapy cycles.

Using FN rates for example can be presented as an aggregate by patient (18/186, 9.84%) or by administered chemotherapy cycles (18/557, 3.23%) before the event occurred. The rates in the current study are higher compared to Jones et al., which had a FN rate of 5% [1], which was higher in patients over 65 (8%) [14]. In addition, this trial enables one to evaluate common toxicities of chemotherapy in a real-world setting as opposed to within the framework of a typical randomised trial with narrower inclusion criteria. This is of note as the existing literature demonstrates that the incidence of FN and complications in a pragmatic trial are higher than those reported in clinical trials [2–5, 17–20]. One of the greatest risks for FN is being aged ≥ 65; in the current study, 22.5% of patients were ≥ 65, compared with 16% in the Jones study [1, 14].

There are acknowledged limitations with the current study. The study is not double-blind so both patients and physicians knew which treatment they were receiving; it was also performed at a limited number of institutions. This latter limitation will be resolved in the expanded study as more institutions are involved. It might be viewed as both a limitation and a positive that the duration of ciprofloxacin and G-CSF was left to physician's choice. This was done to reflect the realities of clinical practice in a real-world setting. As with all studies, one never knows if individual physician biases are affecting which patients they are approaching for the study and those that they are not. Challenges with the data collection process include for example, if a patient went to another health care provider at another institution, whose data was not on the EMR. However, by measuring physician engagement which signals both their willingness to participate and enrol patients, we are hopefully addressing one of the major limiting factors to rapid accrual to clinical trials [21]. Another concern raised by some investigators is the general trend in trying to avoid antibiotic use in the general population. Of note, this study reported two cases of *Clostridium difficile* infection, and both were in patients in the G-CSF arm.

In conclusion, optimising primary FN prophylaxis for patients receiving TC chemotherapy may offer not only cost savings, but also may improve patient comfort and acceptability. In order to answer these important, pragmatic questions, a novel method to allow comparison of established standards of care is needed as part of an increasing internationally mandated incentive to perform more pragmatic clinical trials. In the current study, we have demonstrated feasibility of a novel trials methodology. Moreover, the incidence of toxicities reported in our study means that a future study to definitively determine the optimal type of prophylaxis will require a large sample size. We are currently conducting such a study, where the primary outcome is to document rates of febrile neutropenia and treatment-related hospitalisation as well as secondary outcomes of rates of chemotherapy dose reduction, delay, and discontinuation [22].

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Compliance with ethical standards

Conflict of interest BH consults for Cornerstore Research. All other authors have nothing to disclose.

Research involving human participants The study was approved by the local Research Ethics Board at each participating centre (The Ottawa Health Science Network Research Ethics Board and Health Research Ethics Board of Alberta).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix 1. Consent script

Multi-centre study to determine the feasibility of using an integrated consent model to compare two standard-of-care regimens for primary prophylaxis of taxotere/cyclophosphamide-induced febrile neutropenia

REaCT-TC OTT 14-03

"Our discussion today is a new approach to informing and consenting patients to participate in this study. The traditional approach is to provide a paper copy of the detailed information sheet and consent form for you to sign. Using this integrated model for consenting we will have a discussion and you may give a verbal consent to participate or not to participate. I will document our discussion and your decision in your progress notes that are part of your health records.

As we've talked about, you will be receiving four cycles of taxotere and cyclophosphamide chemotherapy for your breast cancer. Because this chemotherapy can cause low white cell counts, it increases your risk of infections. We therefore give patients medications to reduce the chance of this happening. I can treat you with either a drug called G-CSF or a drug called ciprofloxacin. GCSF and Ciprofloxacin have considerably different costs that ultimately impact our health care system. They're both approved by Health Canada and I commonly use either one of them in patients to reduce the chance of infections with chemotherapy. G-CSF is given as a daily injection at home during the 4 cycles and ciprofloxacin is a tablet that you take twice a day at home starting 5 days after chemotherapy for 14 days of each of the 4 cyclesThey can both have side effects that are potentially mild and are significantly less than those that the chemotherapy causes. There are no common side effects of taking G-CSF however a less common side effect could be brief pain at the injection site and sometimes muscle aches. The most common side effect of Ciprofloxacin is diarrhea which can be easily treated with anti-diarrhea medication. Because we really don't know if one is better than the other, some of the Oncologists at The Ottawa Hospital Cancer Centre (TOHCC) are doing this study by randomly (like a flip of a coin, so that we can obtain an unbiased answer) giving participants one or the other drug and then comparing results over a period of 1 year. We are also looking at how feasible it is for study doctors to enter participants on this study using this integrated consent model. If you choose to participate there won't be any special procedures or visits and you will receive a copy of this document for your reference.

If you do participate and decide to stop your participation in the study you may do so and we can discuss together how to proceed, likely this would mean switching to the other drug that was not assigned to you.

At the end of the study, there will be a satisfaction survey for you to complete.

Your participation in this study is voluntary. If you choose not to participate, your decision will not affect the care you receive at this institution at this time, or in the future. You will not have any penalty or loss of benefits to which you are otherwise entitled to.

All research-related records will be kept for 10 years after termination of the study. No identifiable information will leave this institution. The study sponsor Dr. Clemons located at TOHCC, The Ottawa Hospital Science Network Research Ethics Board (OHSN-REB) and the Ottawa Hospital Research Institute may review your relevant study records for audit purposes.

If you have any questions about this study please refer to your list of contact numbers to reach me. The OHSN-REB has reviewed this protocol. The Board considers the ethical aspects of all research studies involving human participants at the Ottawa Hospital Cancer Centre. If you have any questions about your rights as a study participant, you may contact the Chairperson at XXX.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Do you have any questions?"

Appendix 2. Patient satisfaction survey

REaCT OTT-14-03 Participant study #_____

Patient Satisfaction Survey						
	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**	**Not Applicable**
The clinical trial was explained clearly to me by my oncologist.						
I thought that the questions I had about the clinical trial were answered to my satisfaction						
If I was asked to participate in this study again, I would say yes.						
I found that taking part in this study interfered with my quality of life.						
I found that it was time-consuming to take part in this study.						

Additional comments:

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