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CLINICAL TRIAL

A multicentre, randomized pilot trial comparing vascular access strategies for early stage breast cancer patients receiving non-trastuzumab containing chemotherapy

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Abstract

Purpose All vascular access strategies foradministering chemotherapy in early stage breast cancer (EBC) are associated with risks and benefits. As the most effective type of access is unknown a feasibility trial, prior to conducting a large pragmatic trial, was undertaken.

Methods The trial methodology utilized broad eligibility criteria and the integrated consent model incorporating oral consent. EBC patients receiving non-trastuzumab-containing chemotherapy were randomized to peripheral access or central line insertion. The a priori definition of feasibility was: > 25% of patients approached agreed to randomisation and > 25% of physicians approached patients. Secondary outcomes included rates of line-associated complications.

Results Of 159 patients approached, 150 (94.3%) agreed to randomisation, 77 (51.3%) were randomized to peripheral and 73 (48.7%) to central access. 6/26 (23.1%) of medical oncologists approached patients. Rates of complications per chemotherapy cycles in the peripheral vs central access groups with risk difference (RD) (95% CI) were: thrombotic events requiring anticoagulation [1 (0.3%) vs. 3 (1.0%), RD −0.7(−1.9,0.5)], line infections [0 (0%) vs. 1 (0.3%), RD −0.3(−0.9,0.3)], phlebitis [2 (0.6%) vs. 0 (0%), RD 0.3(−0.3,0.8)], and tissue infiltrations [4 (1.1%) vs. 1 (0.3%), RD 0.8(−0.4,2.1)]. Overall, 8.0% (6/75) and 7.7% (5/65) of patients had at least one of these complications in the peripheral and central access arms respectively [RD −0.9(−9.4,7.6)]. The study was terminated early due to slow accrual.

Conclusion While meeting its a priori feasibility criteria for patient engagement, the slow accrual means that conducting a large pragmatic trial would require overcoming the barriers to physician recruitment.

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Keywords Vascular access · Integrated consent model · Breast cancer · Chemotherapy

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Background

There are a number of vascular access strategies for patients receiving intravenous (IV) chemotherapy for early stage breast cancer (EBC). These include; peripheral access through a vein, or central access either through a peripherally inserted central catheter (PICC) or a totally implanted vascular access device (i.e. PORT). Each type of access strategy has its own risks, benefits and associated costs to both the patient and the healthcare system [1, 2]. Despite the large number of patients receiving chemotherapy for EBC, surveys of patients and healthcare providers show that significant variability exists in the use of peripheral versus central venous access strategies for patients undergoing chemotherapy [3, 4].

Factors affecting the type of access chosen can be patient, provider, regimen, and institutional related. Patient factors include preference for intermittent cannulation versus the constant presence of a device, and quality of venous access. Regimen factors include the duration and frequency of chemotherapy and type of chemotherapy (anthracycline or non-anthracycline). Institutional factors include access to services for insertion, and policies regarding phlebotomy from central devices. Provider factors include the ability of staff to locate and cannulate veins for peripheral access, and physician beliefs about safety and risks of each strategy. Reviewing the literature comparing the risks (e.g. thrombosis and infection rates) and benefits (e.g. improved patient quality of life) of different vascular access strategies is challenging. Most studies are small and retrospective, include a small proportion of breast cancer patients or evaluate patients with lines inserted for antibiotic administration as well as the use of different patient-reported outcome measures [1, 2, 5].

The variability in practice likely reflects the different risk–benefit assessments by physicians and patients, which provides evidence of clinical equipoise. This has implications for cost, side-effects, and optimal patient care. While determining the optimal vascular access strategy remains an important medical issue for patients, nurses, physicians and society, performing such a trial using the traditional clinical trials model would be challenging. Our team has been evaluating innovative trial designs for comparisons of standard of care interventions that are pragmatic, inexpensive and practical [6].

In the current study, we assessed the feasibility of performing a future large pragmatic, multicentre randomized clinical trial using this novel trial methodology. In this pilot study, we compared peripheral versus central access in patients receiving non-trastuzumab-containing chemotherapy regimens for EBC.

Methods

Study population

Patients with newly diagnosed Her2-negative breast cancer, who had received no prior chemotherapy and were planned to receive a standard neo/adjuvant chemotherapy regime) were eligible. Patients had to be able to provide verbal consent and were excluded if there was a contraindication to central line placement. The study was approved by the provincial Research Ethics Board (Ontario Cancer Research Ethics Board, OCREB) and local REBs. The trial was registered on clinicaltrials.gov [7].

Trial design and randomization

In this multicenter and unblinded trial, eligible and consented patients were stratified based on anthracycline use or not, and randomized before starting chemotherapy using permuted variable blocks of 3 and 6 via a computerized randomization system developed by the Methods Centre in Ottawa. Randomization was to either peripheral access or to have a central line inserted. The choice of central device (i.e., PICC versus PORT) was left to the patient and physician.

Consent process

The rethinking clinical trials (REaCT) Program was developed for comparing standard of care interventions and is outlined elsewhere [6]. The key components include: selection of clinically relevant and practical questions; demonstration of clinical equipoise through surveys of knowledge users [3, 4] and completion of systematic reviews [8], simply defined study endpoints, use of an integrated consent model (ICM) incorporating oral consent [9]; efficient REB approval [10], and web-based randomization in the clinic. While the REaCT consent process that includes the ICM, and in particular, oral consent has been successfully used in studies comparing systemic therapies [6], the current study was designed to demonstrate whether such a methodology was feasible for future multicenter trial to be performed.

Data collection

Outcome data were collected from both the physician using an email template sent by the research associate when the patient returned to clinic after each chemotherapy treatment and through the patient's electronic health record.

Outcomes

Primary outcomes: feasibility

Trial feasibility was evaluated through a combination of endpoints. These included; patient engagement (the percentage of patients approached who agreed to randomisation) and physician engagement (percentage of medical oncologists who agreed to participate in the trial compared to the percentage who approached patients regarding the trial). Other endpoints that would allow planning for a future larger pragmatic trial included; time for local or provincial REB approval, accrual rates (i.e. percentage of patients who receive (neo)adjuvant IV non-trastuzumab containing chemotherapy compared to the number of participants who were approached) and patient adherence with randomization allocation (percentage of patients and are randomized who accept their randomization arm).

Secondary outcomes: clinical

Secondary outcomes included access-associated complications. These complications included rates of infections (line infections, skin infections, or systemic infections including febrile neutropenia), rates of thrombotic complications, rates of anticoagulation, rates of upper extremity ultrasound testing, extravasation rates, thrombolytic usage, treatment delays related to vascular access, and rates of line discontinuation. Extravasation was defined as when a vesicant medication (e.g. doxorubicin or epirubicin) leaks out of a vein potentially causing blistering and other tissue injuries to the surrounding area. Infiltration was defined as when a non-vesicant fluid leaks out of a vein [11]. For patients randomized to peripheral access, information on the number of attempts at cannulation was collected as well as the site of cannulation (i.e. ipsilateral to surgery vs contralateral to breast surgery). The percentage of patients randomized to the peripheral access arm who subsequently require a central line to be inserted was also calculated.

Sample size and statistical analysis

The a priori criteria that needed to be met to deem this feasibility trial successful were if > 25% of appropriate patients who were approached about the study and agreed to participate and if > 25% of physicians who agreed to participate in the study did approach patients for the study. If these feasibility endpoints were met, we planned to expand the study to provide appropriately powered data for to evaluate access-associated complications. As this was a feasibility study there was no pre-defined sample size, however, it was pragmatically defined as the sample size reached after 1 year of accrual to demonstrate feasibility of accrual. We anticipated that around 100 patients would be entered per study arm. Feasibility outcomes are presented descriptively. For inferential analyses of clinical outcomes, relative risks with 95% CIs were calculated.

Results

The study ran from April 19, 2016 to October 10, 2018. The study consort diagram is shown in Fig. 1. Of 150 patients randomized, 77 (51.3%) were randomized to peripheral access and 73 (48.7%) to central access. Data were available for analysis for all 150 randomized patients. The baseline characteristics of the randomized patients are shown in Table 1. Median age was 57 years (range 24–89). The most commonly used regimens were; docetaxel/cyclophosphamide (65/150, 43.3%), FEC-Docetaxel (44/150, 29.3%) and dose-dense AC-Paclitaxel (41/150, 27.3%). For patients randomized to central line insertion, and in whom a line was actually inserted ($n = 64$) this was a PICC in 100% of cases and the line was inserted in the ipsilateral arm to surgery in 11/64 (17.2%) and the contralateral arm in 53/64 (82.8%) of patients. The mean/median number of days between the date of randomization and date of line insertion was 7 (IQR 6-12), with 6 patients who randomized to central line having their first cycle of chemotherapy through peripheral vein and their central line inserted before their second cycle of chemotherapy. One additional patient had her first cycle administered peripherally, but following chemotherapy-associated complications, chemotherapy was discontinued before a PICC could be inserted.

Primary outcome measures: feasibility

Patient engagement

Of 159 potentially eligible patients who were approached for the study at the 3 study sites, 150/159 (94.3%) agreed to randomization. Of the 9 approached patients who declined study entry, 4 provided specific reasons for declining including; feeling a central line would interfere with their lifestyle ($n = 2$), wanting to try peripheral access first ($n = 1$) and advised by family/friends to get a central line ($n = 1$).

Physician engagement

Of 26 physicians who initially agreed to participate in the study, 6 (23.1%) approached patients for the study (2/11 in Ottawa, 3/7 in Kingston and 1/8 Edmonton).

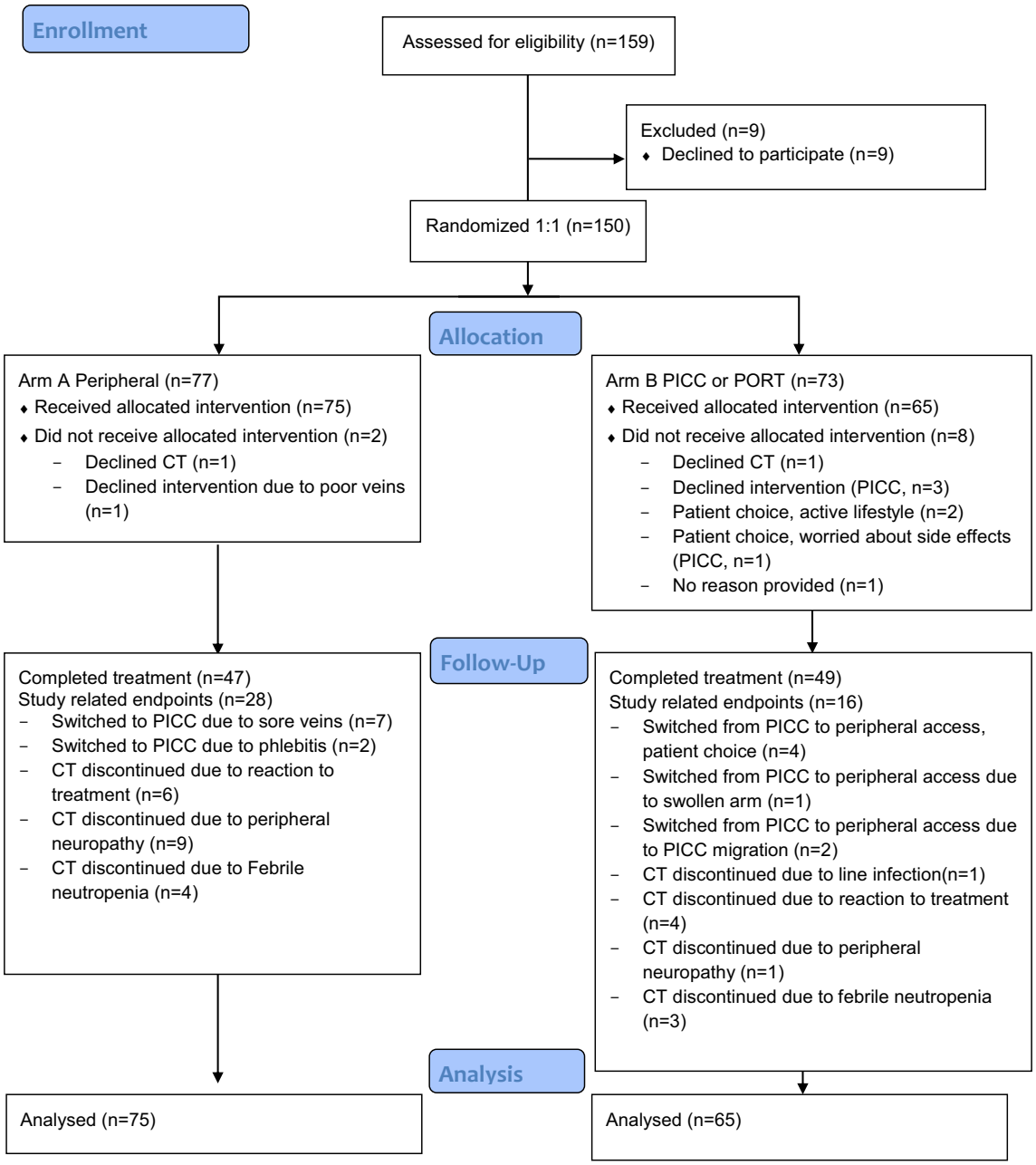

Fig. 1 Consort diagram

Time for local or provincial research ethics approval

The regulatory aspects of opening a REaCT trial are outlined elsewhere [6]. As the Ottawa and Kingston centres are in the province of Ontario, the protocol was submitted to the Ontario Cancer Research Ethics Board (OCREB) first. OCREB approval took 2 months. Following provincial approval, the protocol requires approval at each study site, the individual sites had to then complete contracts and have site initiation visits. Thus, the time from initial REB submission to study opening was 5 months in Ottawa, 7 months in Kingston and 14 months in Edmonton.

Accrual rates

Data on the number of patients receiving chemotherapy (and therefore potentially eligible for the study) from the time of study opening until closure was only available for 2 sites. During the time that the trial was open to accrual, 775, and 134 patients received a non-trastuzumab-containing

Table 1 Baseline demographics for randomized participants

	Peripheral $n=77$	Central $n=73$	Total $n=150$
Age median (range)	57 (24–81)	56 (28–89)	57 (24–89)
Stage *n* (%)			
1	12 (15.6%)	17 (23.3%)	29 (19.3%)
2	43 (55.8%)	33 (45.2%)	76 (50.7%)
3	22 (28.6%)	23 (31.5%)	45 (30.0%)
Chemotherapy regimen *n* (%)			
TC	28 (36.4%)	37 (50.7%)	65 (43.3%)
FEC-D	25 (32.5%)	19 (26.0%)	44 (29.3%)
dd AC-P	24 (31.2%)	17 (23.3%)	41 (27.3%)
Type of central line inserted, *n* (%)			
PICC	–	73 (100%)	
PORT	–	0 (0%)	
For patients randomized to central line ($n=73$)			
Days from randomization to line insertion: n (range)	–	7 (2–37)	
Site of central line insertion, *n* (%)			
Ipsilateral to surgery	–	11 (15.1%)	
Contralateral to surgery	–	53 (72.6%)	
No line inserted	–	9* (12.3%)	

TC taxotere/cyclophosphamide×4; *dd AC-P* 2-weekly dose-dense AC×4, then paclitaxel×4; *FEC-D* 3-weekly FEC×3, Docetaxel

*Includes 1 patient who had cycle 1 through a peripheral vein then stopped chemotherapy before a PICC could be inserted

neo/adjuvant chemotherapy regimen in Ottawa or Kingston respectively. Of these potentially eligible patients, 147/775 (19%) in Ottawa and 11/134 (8.2%) in Kingston were approached to participate. This was 17% (158/909) of patients seen at these 2 sites. In Edmonton, the trial was open for 11 months, during which 89 patients were flagged for eligibility, however, only 1 patient was approached to participate.

As the resulting rate of accrual was slower than anticipated with 150 patients accrued over 31 months, when it was initially projected to be 200 patients in a year, the decision was made to close the trial after 150 patients were enrolled.

Patient/physician adherence to randomisation allocation

Of 77 patients randomized to the peripheral access arm, 2 (2.6%) patients declined their randomisation arm because they either decided not to have chemotherapy ($n=1$) or were advised to get a PICC due to "poor veins" ($n=1$). Of 73 patients randomized to the central access arm, 8 (11%) patients declined their randomization arm. The reasons for declining their study arm were: patient decided not to have chemotherapy ($n=1$), decided they did not want a PICC ($n=3$, one patient had one cycle of chemotherapy without the PICC as they were awaiting PICC insertion and then decided not to have a line inserted, 2 patients decided against PICC due to their active lifestyle), worried about side-effects associated with PICCs ($n=1$) and no reason provided ($n=1$). All physicians adhered to their patient's allocated study arm.

Secondary outcomes

Access-associated complications

For access-associated complications, the results are presented by the number of cycles of chemotherapy administered. The rates of thrombotic complications requiring anticoagulation in the peripheral vs central access groups with risk difference (RD) (95% CI) were; [1 (0.3%) vs. 3 (1.0%), RD −0.7(−1.9,0.5)] (Table 2). The thrombotic events were 1 case of superficial thrombophlebitis in the peripheral access group and 2 DVTs and 1 pulmonary embolus in the central line group. Other complications in the peripheral vs central access groups with risk difference (RD) (95% CI) included; line infections [0 (0%) vs. 1 (0.3%), RD −0.3(−0.9,0.3)], phlebitis [2 (0.6%) vs. 0 (0%), RD 0.3(−0.3,0.8)], and infiltrations [4 (1.1%) vs. 1 (0.3%), RD 0.8(−0.4,2.1)], in the peripheral access versus central groups, respectively (Table 2). There were no extravasations, however, the one patient in the central line group who had an infiltration had this with their first cycle of chemotherapy

Table 2 Study outcome data presented by number of cycles of chemotherapy administered

	Total	Peripheral access *n* (%)	Central access *n* (%)	Risk difference (95% CI)
Number of chemotherapy cycles administered	663	350	313	
Venous thromboembolism (VTE)	3 (0.6%)	0 (0.0%)	3 (1.0%)	−1.0 (−2.04, 0.12)
Type of VTE*				
DVT	2 (0.3%)	0 (0%)	2 (0.6%)	
PE	1 (0.15%)	0 (0%)	1 (0.3%)	
Other thrombotic events	2 (0.3%)	2 (0.6%)	0 (0.0%)	0.57 (−0.22, 1.36)
Type of other TE events				
Line thrombus	0 (0%)	0 (0%)	0 (0%)	
Phlebitis	2 (0.3%)	2 (0.6%)	0 (0%)	
Thrombotic events requiring anticoagulation	4 (0.6%)	1 (0.3%)	3 (1.0%)	−0.67 (1.89, 0.54)
Infections (total)	29 (4.4%)	11 (3.1%)	18 (5.8%)	−2.61 (−5.77, 0.55)
Type of infection				
Line infections	1 (0.15%)	0 (0%)	1 (0.3%)	
Skin infections	7 (1.1%)	3 (0.9%)	4 (1.3%)	
FN or sepsis	9 (1.4%)	6 (1.7%)	3 (1.0%)	
Other	12 (1.8%)	2 (0.6%)	10 (3.2%)	
Skin extravasations	0 (0%)	0 (0%)	0 (0%)	
Skin Infiltrations	5 (0.75%)	4 (1.1%)	1** (0.3%)	0.8 (−0.4, 2.1)
Upper limb/lower limb ultrasound for potential VTE				
Yes	11 (1.7%)	4 (1.1%)	7 (2.2%)	−1.1 (−3.1, 0.9)
Upper limb	8 (1.2%)	4 (1.1%)	4 (1.3%)	
Lower limb	3 (0.4%)	0 (0%)	3 (1.0%)	
Chest X-ray performed[+]	52 (7.8%)	23 (6.6%)	29 (9.3%)	−2.7 (−6.8, 1.4)
Reason for chest x-ray				
After insertion to check line position	21 (3.2%)	8 (2.3%)	13 (4.2%)	
Subsequently to evaluate line migration	1 (0.15%)	0 (0%)	1 (1.4%)	
Other reason[++]	30 (4.5%)	15 (4.8%)	15 (4.8%)	

VTE venous thromboembolism; *DVT* deep vein thrombosis; *PE* pulmonary embolism; *TE* thromboembolic; *FN* febrile neutropenia

*Patients can have more than one complication

**Infiltration occurred after cycle 1 before their PICC was inserted

[+]Patients in PICC-inserted group having a placement CXR before chemo started will not have this CXR recorded as it falls outside of data collection period

[++]Other reasons included: rule out pneumonia, check for cardiopulmonary disease, check for metastasis

and before the line was inserted. Overall, 8.0% (6/75) and 7.7% (5/65) of patients had at least one of these complications in the peripheral and central access arms, respectively [RD −0.9(−9.4,7.6)].

The rates of additional imaging (beyond routine chest x-rays for checking the position of PICCs immediately after insertion) included upper extremity ultrasounds [4 (1.1%) vs. 4 (1.3%) RD −0.14(−1.8,1.5)] in the peripheral versus central access groups, respectively. In the peripheral access group, the reported reasons for ordering these ultrasounds were; superficial thrombophlebitis ($n=1$), cellulitis ($n=1$, no clot seen), swollen arm ($n=2$, no clot seen). In the central access group, the reported reasons were; neck pain ($n=1$, confirmed DVT), pain around PICC insertion ($n=1$, confirmed DVT), device insertion ($n=2$). Additional chest X-rays were performed in 23 (6.6%) vs. 29 (9.3%) [RD −2.7(−6.8,1.4)] cycles in the peripheral vs central access groups, respectively. For the peripheral access patients, 8 patients who were randomized to the peripheral access group but then subsequently had a PICC inserted had chest X-rays performed to confirm the line position (1 patient switching from peripheral to PICC did not have an x-ray). Fifteen chest X-rays were performed to rule out chest infections when patients went to the ER or were hospitalized. In the central access group, 13 were performed to confirm line position, 1 for line migration check and 15 for other reasons such as to rule out chest infections.

The consequences of complications in the PICC group included; PICC removal and receiving rest of chemotherapy through a peripheral vein (7 patients, 9.6%), line removed and replaced with same type of line i.e., a PICC (2 patients, 2.7%) and line removed and replaced with another type of line i.e., a PORT (1 patient, 1.4%). When evaluated by the total number of cycles of chemotherapy, PICC migration complicated 17 cycles (5.4%), while Cathflo was required in 2 (0.6%) cycles.

Percentage of patients changing the type of access after chemotherapy started

The number of patients who were randomized to peripheral access who subsequently required a central line was 9/77 (11.7%). The reasons for having a central line inserted were, "poor veins" in 7 cases (9.1%) and phlebitis in 2 cases (2.6%). Of 73 patients randomized to receive a central line, 7/73 (9.6%) had the line removed early (i.e. before completion of chemotherapy). The reasons included patient choice ($n=4$), PICC migration ($n=2$), and a swollen arm ($n=1$), imaging confirmed this was not a DVT. These 7 patients went on to receive their chemotherapy through a peripheral vein. Nine (9/73, 12.3%) patients in the PICC arm discontinued chemotherapy early due to febrile neutropenia ($n=3$), repeated hospitalisations ($n=1$), body pain ($n=1$), nausea ($n=1$), line infection ($n=1$), peripheral neuropathy ($n=1$), planter fasciitis ($n=1$). Once these patients discontinued chemotherapy their lines were removed.

Number of attempts at cannulation

For those patients randomized to peripheral access over 350 cycles of chemotherapy, the mean number of attempts at cannulation to administer chemotherapy was 1.3 (range 1–6). The site of cannulation was the ipsilateral arm in 112 cycles (32%) and 214 cycles (61.1%) in the contralateral arm to breast surgery. The results are unknown for 10 cycles of chemotherapy and excluded 14 cycles of chemotherapy in 3 patients with bilateral disease.

Discussion

Despite the widespread use of intravenous chemotherapy in patients with early stage breast cancer, the optimal route of venous access remains unknown. Each has its advantages and disadvantages. While the use of a peripheral vein is usually straight forward, it does not reduce the need for extra peripheral IV attempts for blood counts. While vascular access devices may reduce the risk of chemotherapy extravasation and vein sclerosis (e.g. from anthracyclines [12–16]), they can result in delays in beginning therapy while waiting for the insertion, as well as being associated with an increased risk of infections and blood clots [17]. PICC use may limit physical activities and necessitate precautions during bathing to avoid getting the dressing wet and they can occlude and migrate, while PORTs require monthly flushing when not used routinely and can also become occluded. PORT insertion and removal is a procedure that is often performed by either a surgeon or interventional radiology and requires another incision.

A recent systematic review confirmed the paucity of data from definitive randomized trials in the setting of venous access for routine administration of chemotherapy [8]. Another review evaluated the risks and benefits of types of central lines in breast cancer patients focused on types of central lines, not the presence or absence of one [2]. This lack of guidance is also reflected in surveys of patients and healthcare providers that have shown considerable clinical equipoise not only in the type of access with different chemotherapy regimens but also with the same regimen [3, 4]. In the current study, we sought to answer this important clinical question.

A combination of different endpoints were used to demonstrate the feasibility of performing this novel trial methodology, with the plan of performing a future larger trial with efficacy endpoints. It was evident that despite the efficiency of regulatory approval for opening the trial being similar to that for more conventional trials, and excellent patient/physician adherence to the randomized arm, that only a relatively small proportion of patients (158/909, 17%) being treated with neo/adjuvant systemic chemotherapy in the 2 study sites with available data, were approached by their oncologists for participation in the study. Despite the initial interest of 26 medical oncologists, only 6/26 (23.1%) of them approached patients for this study. A series of strategies were implemented to improve accrual, including frequent email reminders from the research team and the Division head, and verbal reminders about the trial at monthly research rounds. The perception at one site was that, "no one was interested", one physician cited that, "I tried to accrue two patients and failed at both as the nurses talked them into having central lines. No one else even tried".

Our pilot study is the largest trial performed to date evaluating different types of venous access and the rates of complications associated with using the peripheral and central routes. These rates of complications appear similar to those reported in the literature [1, 2, 12–18]. Clearly, however there are acknowledged limitations with the current study. The study was relatively small and open label. A further challenge was the slower than anticipated rate of accrual to the trial, likely reflecting the challenge of engaging physicians in studies where they, "already know what best care is", that led to the study closing before completing accrual. However, this does not take away from the fact that this is

the only randomized trial we could identify to guide clinical practice. The study was multicentre and the types of chemotherapy given reflect modern breast cancer practice. Future studies are needed to evaluate the complication rates of different modes of venous access. However, given the relatively low rates of complications reported in our study, these studies would require significant sample sizes.

Despite the low rates of physician engagement, the topic of venous access remains important to patients, physicians and healthcare providers/systems [3, 4]. What is evident is that patient engagement is very high and that the rates of complications associated with peripheral and central access are similar. Patient engagement was 94.3%, showing that patients do want to have these important practical questions answered. In addition, with respect to the line complications, the nature of these differ, for example, line-associated thrombosis is potentially fatal, while peripheral vein phlebitis can cause prolonged discomfort. From an economic standpoint in centres where the majority of patients have lines inserted, the finding that 11.7% of patients randomized to peripheral access who subsequently had a central line inserted would suggest that close to 90% of patients can be safely treated without a central line. While larger studies are required to address many unanswered questions, such trials would require implementation science expertise to identify barriers and potential facilitators.

In conclusion, optimizing the type of intravenous access may offer not only cost savings, but also improve patient comfort and acceptability. 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 clinic trials. In the current study, we have demonstrated the feasibility of a novel trials methodology in terms of patient engagement. However, given the generally low level of physician engagement performing such a trial may be challenging. As such, future work in understanding and addressing these barriers to increase physician participation is necessary before embarking on larger trials.

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Compliance with ethical standards

Conflict of interest Dr. Awan reports participating in the Novartis Canada Advisory Board on the use of Ribociclib. Dr. Hutton reports personal fees from Cornerstone Research, outside the submitted work. The remaining authors declare that they have no conflicts of interest (Robinson, Stober, Fergusson, Kehoe, Bedard, MacDonald, Brunet, Saunders, Mazzarello, Vandermeer, Joy, Basulaiman, Mallick, and Clemons).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national 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.

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