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CLINICAL TRIAL

Creating a pragmatic trials program for breast cancer patients: Rethinking Clinical Trials (REaCT)

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Abstract

Background The proportion of breast cancer patients enrolled in clinical trials is falling. The Rethinking Clinical Trials (REaCT) program was developed to challenge some of the contemporary barriers responsible for this fall in accrual. In this article, we review the successes and challenges our program has faced.

Methods The REaCT program was created to improve care and outcomes for cancer patients through surveys of patients and healthcare providers, systematic reviews, economic evaluations, and the performance of pragmatic randomized trials with patient-centered outcomes. Likely, the greatest difference to conventional trial methodologies has been our widespread use of the integrated consent model (ICM) incorporating oral consent.

Results Between 2014 and 2018, the program has recruited over 2000 patients to 15 randomized studies at 11 Canadian cancer centers. The REaCT program has completed and published five patient surveys, six healthcare provider surveys, ten systematic reviews, performed four economic evaluations, opened 15 clinical trials comparing standard of care interventions (two surgical, two adjuvant chemotherapy, five adjuvant supportive care, one radiology, two vascular devices, two palliative supportive care, and one molecular diagnostics). Patient surveys have shown high levels of satisfaction with the ICM.

Conclusion The REaCT program was developed to tackle important practice questions that will better guide optimal practice and to increase the availability of pragmatic clinical trials. While many challenges remain, future strategies will involve including more study sites and efforts to integrate novel information technology strategies.

Keywords Pragmatic trials · Clinical trial accrual · Integrated oral consent · Patient-centered outcomes

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Background

Despite the increasing prevalence of cancer, expanding budgets, increased availability of effective treatments, the number of patients participating in interventional cancer clinical trials continues to fall [1]. Even with 75% of patients expressing a willingness to participate in cancer research, the accrual of adult cancer patients to clinical trials has fallen from 12% in 2007 to 7% in 2017 [1–4]. The reasons for this fall are likely multifactorial, and can be divided broadly into physician/investigator-specific, patient-specific, clinical trial-specific, and institutional/network-specific barriers (Table 1) [5–7].

The consequences of poor accrual include failing to meet recruitment goals, early trial termination, and inconclusive results [8]. Another consequence of fewer trials being performed is that cancer patients are often faced with multiple,

Table 1 Barriers to clinical trials participation [4–8, 40, 41]

Investigator/physician specific
• Willingness to be involved in or refer a patient
• Lack of knowledge about clinical trials
• Concern regarding patient's ability to participate
• Negative effect of physician–patient relationship
• Informed consent time consuming
• Strict schedule to follow
• Inclination towards a treatment in clinical trials
• Lack of incentives
Patient specific
• Difficulty understanding "legal" consent forms
• Fear of experimentation "randomization"
• More frequent visits
• Unaware of trial availability
• Distrust of medical science
• Age—older made more comorbidities therefore excluded
• Travel burden
• Lack of family support
Clinical trial specific
• Complicated, redundant paperwork and regulatory process
• Delay of ethical research board response
• Strict eligibility criteria
• Written consent process
• Placebo/no-treatment arms
• Side-effects
• Treatments with limited efficacy
Institutional/network barriers
• Clinical space and time
• Dedicated research staff
• Funding
• Availability of clinical trials
• More focused towards academic than community center

"reasonable" treatment options without appropriate high-quality evidence to guide their choices [9]. This is despite the efforts of national bodies (e.g., SPOR in Canada, PCORI in the US, and NIHR in the UK) to fund comparative effectiveness trials. The Rethinking Clinical Trials (REaCT) program was conceived and developed to improve care and outcomes for cancer patients by establishing collaboration between patients, researchers, and healthcare providers [9]. Specifically, its mandate was to build and promote a platform that would tackle the issues of a dearth of academic oncology trials being performed, poor accrual in trials that were being conducted, and the ongoing challenges of performing research in an environment of reduced research funding.

Ultimately, we hope, through these efforts and approaches, that other investigators will develop their pragmatic patient-centered trials so that we can all strive to improve patient care. We have previously outlined our methodology for establishing the REaCT program [9]. This update will evaluate the successes and challenges implementation has faced.

Methods

The REaCT processes have been reviewed elsewhere and can be broadly divided into ten facets (summarized in Fig. 1). While not all REaCT studies can or should follow all these tenants, we strive to achieve as many of them as possible (Table 2). We will present each of these goals in addition to how we have achieved them, as well as future and ongoing challenges.

Results

Selection of clinically relevant questions through surveys of patients and other end users

REaCT trials attempt to address questions of practical importance for patients, their families, and healthcare providers. This includes identifying areas of clinical equipoise, defined as the uncertainty among the medical community about the risks and benefits of interventions. Ultimately clinical equipoise provides the ethical justification for proceeding with a randomized trial [10, 11]. To date, we have tried to identify important equipoise through; clinical experience, recurring questions in multidisciplinary breast oncology rounds, and through surveys of patients and healthcare providers. Surveys also enable identification of different standard of care options and to define endpoints for trials and to determine the statistical difference in results that physicians would be required to change in practice [12–14]. Due to the practice patterns of the physicians involved in the REaCT program, most of these areas addressed are related to breast cancer management, and we have published five patient surveys and six physician surveys of which two included oncology nurses and pharmacists. The primary obstacle to performing surveys is often the low response rates, something we have improved with the offer of a coffee voucher to responding healthcare providers [15–17].

Surveys of patients

An example of a patient survey that helped the design of a trial evaluated the duration of filgrastim use in patients receiving chemotherapy for breast cancer, as this issue was raised in an earlier chart review [13, 18]. The survey showed that filgrastim use was not only associated with significant issues of bone pains and myalgias, but that, despite its use, nearly half of patients either had febrile neutropenia and/

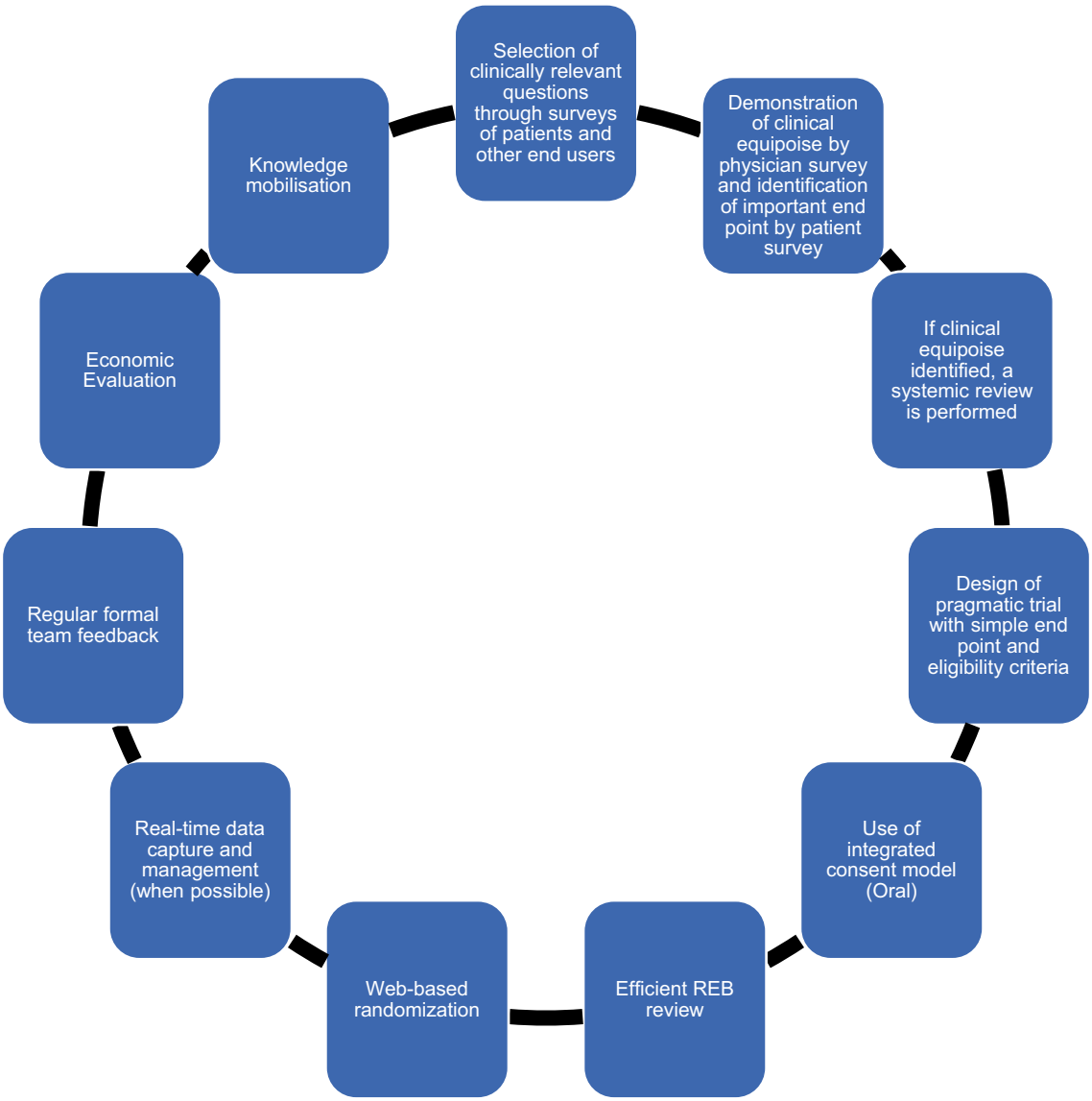

Fig. 1 The REaCT program process

or a chemotherapy dose delay/reduction or discontinuation [13]. The survey showed equipoise in the number of days of filgrastim prescribed. These findings in part led to the design and performance of the REaCT-G trial comparing 5 versus 7 or 10 days of filgrastim, with the primary endpoints that patients said were of most importance to them (i.e., febrile neutropenia rates and treatment-related hospitalizations) [14].

Surveys of healthcare providers

Surveys of healthcare professionals have been used to establish whether clinical equipoise exists, and also to identify trial endpoints of importance to them and to assess interest in terms of whether they would want to open these potential trials at their centers. We have also used surveys to understand the reasons for poor accrual in open trials and to explore strategies they think might help with patient enrollment. In situations where it was evident that, despite the results of previous studies and surveys showing enthusiasm for a prospective trial, survey results were used to close a trial prematurely when it was apparent that full accrual would not be reached [19–23].

Systematic reviews

Once a clinically important question is identified, a systematic review is usually conducted to assess whether past studies have addressed it and to synthesize their findings if available. A major challenge has been that, despite publishing

Table 2 REaCT Trial Portfolio including current enrolling, closed, and published REaCT studies

Study	Brief summary
Open trials	
REaCT-EF [42]	Compare two standard of care schedules for monitoring cardiac function (3 vs. 4 months) in patients receiving trastuzumab for early stage breast cancer
REaCT-TC2 [43]	Compare G-CSF to antibiotics (ciprofloxacin) for primary prophylaxis of Taxotere/cyclophosphamide-induced febrile neutropenia
REaCT-TAPS [37]	Compare a tapering dose of dexamethasone to other standards of care on the presence of taxane-associated pain syndrome (TAPS) in early stage breast cancer
REaCT-ZOL [44]	Comparing a single-dose versus twice yearly Zoledronate for 3 years in patients with early stage breast cancer
REaCT-ILIAD [45]	Evaluate whether adding lower dose olanzapine to standard antiemetic medication can significantly reduce chemotherapy-induced nausea and vomiting in breast cancer patients receiving chemotherapy regimens
REaCT-NSQIP [46]	Evaluate whether adding oral antibiotics or not can a significantly reduce the postoperative surgical infectious complications following colorectal surgery
Trials closed to accrual and pending analysis	
REaCT-VA Her2 Negative [30]	Compare vascular access with either centrally inserted device or through a peripheral vein in patients receiving neo/adjuvant chemotherapy without trastuzumab
REaCT-VA Her2 Positive [29]	Compare vascular access with either a PICC versus PORT in breast cancer patients planned to start trastuzumab based neo/adjuvant therapy
REaCT-G2 [33]	Compare administration schedules of G-CSF (Filgrastim) for primary prophylaxis of febrile neutropenia
REaCT-Mg [47]	Feasibility of using an integrated consent model to compare two oral magnesium supplements for the management of hypomagnesemia from anticancer therapies
REaCT-ADM [48]	Comparing two acellular dermal matrices, Alloderm versus Dermacell in immediate implant-based breast reconstruction
REaCT-BTA [31]	Comparing 12-weekly with 4-weekly bone agents for patients with bone metastasis from breast or prostate cancer
REaCT-DEX [49]	Comparing standard of care schedules of dexamethasone in patients incompletely taking dexamethasone premedication prior to docetaxel chemotherapy
Trials closed and published	
REaCT-TC [12]	Feasibility of using an integrated consent model to compare two standard of care regimens for primary prophylaxis of taxotere/cyclophosphamide-induced febrile neutropenia
REaCT-G [14]	Determine the feasibility of using an integrated consent model to compare standard of care schedules of G-CSF (Filgrastim) for primary prophylaxis of chemotherapy-induced febrile neutropenia in early stage breast cancer
REaCT-TNBC [23]	Determine the feasibility of using an integrated consent model to compare three standard of care regimens for the treatment of triple-negative breast cancer in the neoadjuvant/adjuvant setting
REaCT-Magee [50]	Exploring whether using a validated mathematical equation (the Magee formula) to convert available routine pathology parameters (i.e., ER, PR, Her2, grade, tumor size, and Ki67) into a surrogate Oncotype Dx score will impact on patient care

ten systematic reviews, these reviews have usually identified very little high-quality evidence to drive actual clinical practice [24–27]. For example, following a survey of patients and healthcare providers evaluating different vascular access strategies for patients to receive chemotherapy (peripheral vein vs. peripherally inserted central catheter (PICC) or totally implanted vascular access devices (PORTs)) for breast cancer and the associated complication rates, a systematic review was conducted and revealed no randomized trials in this setting [26, 28]. By identifying clinical equipoise, we have performed two trials to address these gaps [29, 30].

Designing of a pragmatic trial with simple endpoints and eligibility

The REaCT program has deliberately sought to bring together experts in a broad range of research disciplines both inside and outside of oncology. These include expertise in; methodology, biostatistics, health economics, and patient-reported outcomes research. Trial design can vary considerably depending on the question being asked, and the potential number of eligible patients that will be enrolled [31]. If a trial required a large number of patients, a feasibility pilot study was conducted first [12, 14]. These trials used various

combinations of endpoints that have included patient accrual rates, physician engagement, and patient/physician compliance with treatment allocation to evaluate whether expansion to a larger study was viable. If the feasibility endpoints were not met, then no such expansion would occur, and the study would be terminated [23].

As the requirement for additional clinic-based work required by physicians are a deterrent for approaching patients to enroll in trials [32], REaCT trials are designed to have as few requirements as possible, which may slow the physician down in their clinics. The approach therefore includes simple eligibility criteria (often five or less), integrated oral consent, real-time electronic data capture, and having no requirements for additional clinic visits or study-mandated evaluations or procedures. With respect to both inclusion/exclusion criteria and study outcomes, a significant issue with many study designs is the addition of too many superfluous study requirements. These can be driven by either the investigators or through perceived regulatory requirements.

Where there were perceived regulatory criteria that do not improve patient safety, we have increasingly liaised with the appropriate regulatory body to make criteria more sensible. For example, in our study, the requirement for pregnancy tests in patients even if they were postmenopausal and/or not sexually active did not make sense and was often offensive to patients, in addition to adding both costs and unnecessary data. We were able to have this requirement removed in appropriate situations. In order to increase patient enthusiasm for trials, REaCT trial protocols are designed so as to not add any imaging or clinic visits that were beyond the standard of care. For example, patients would complete study questionnaires at home and then return them to the study CRA by mail or at the next scheduled clinic visit. For study endpoints, we used clinically relevant endpoints such as febrile neutropenia rates with G-CSF in REaCT-G2 study [33], and patient-reported outcomes with supportive care interventions or incidence of blood clots when comparing peripheral versus central lines for chemotherapy administration in REaCT-VA studies [29, 30]. Also, to reduce the collection of superfluous data, only toxicity outcomes of interest and relevance to the study were captured.

It is reassuring that, between 2014 and the end of 2018, we opened 15 clinical trials, closed nine trials (Table 2) and recruited 2137 participants (Fig. 2). We have also been able

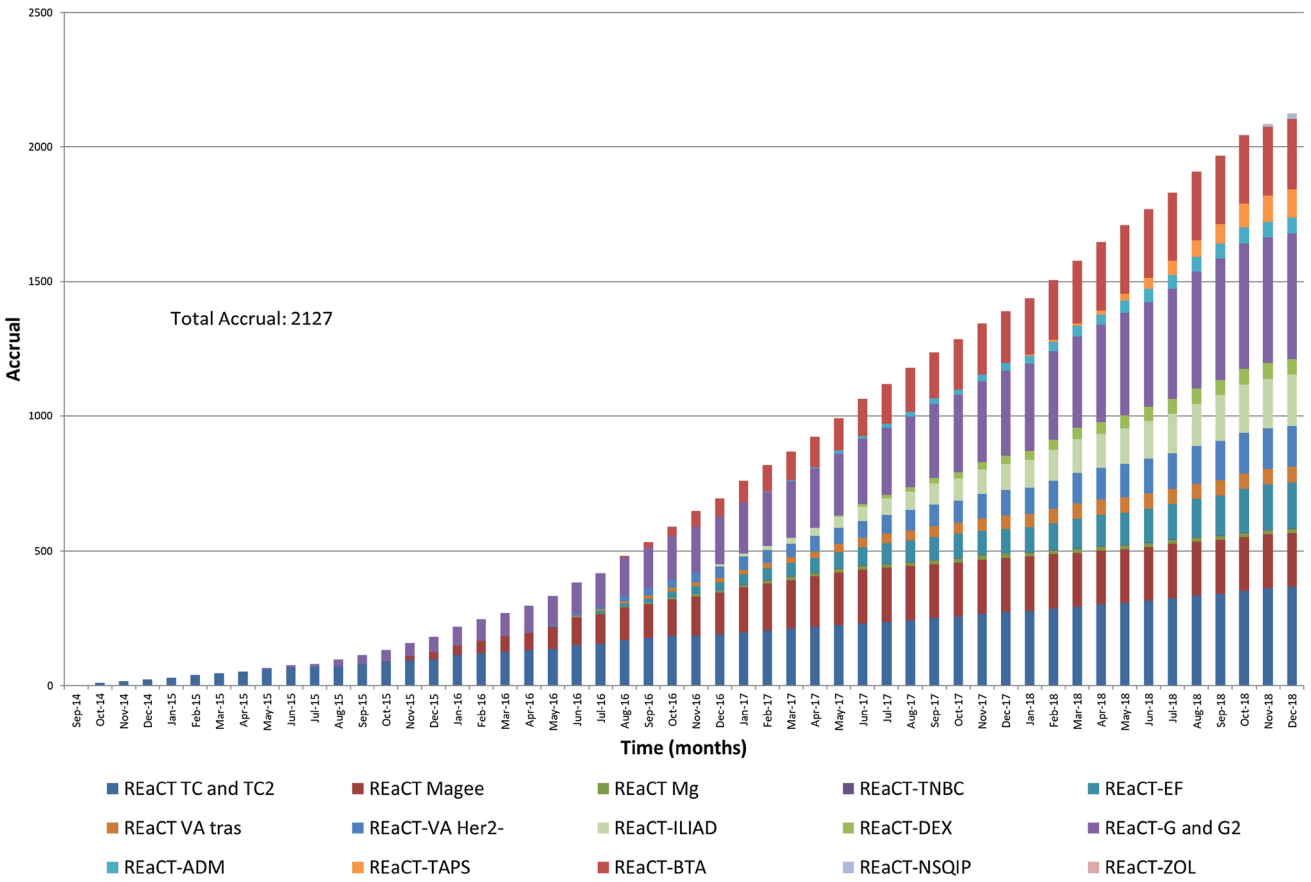

Fig. 2 Cumulative recruitment for each REaCT study from 2014 until the end of 2018

to open trials at eleven centers across Canada, covering both academic and community centers.

Use of integrated consent model (ICM)

For clinical trials deemed "low-risk" by the REB, such as those comparing standard of care interventions, we were able to use the ICM incorporating oral consent. For trials requiring Health Canada oversight such as those evaluating new indications for established agents or trials using a placebo, the ICM could not be used, as written consent is required. The integrated consent process is well described in the literature [34, 35]. Using this model, we can discuss the trial with the patient and answer their questions like a typical clinical interaction. The patient is given a consent template that provides the salient details of the study. Once the patient's questions have been answered, the healthcare provider dictates this conversation into the patient's electronic medical record (EMR). No signed consent form is required, and as the conversation follows that which should be typical in the clinic, there are minimal clinic delays. To date, consent has been obtained by appropriately trained members of the patient's circle of care including physicians, nurses, and CRAs.

Challenges for use of the ICM came from both regulatory bodies as well as investigators. For REB submissions, we would communicate with the REB Chair prior to the protocol being submitted. When making the submission, we commonly attach pivotal papers outlining the ICM and its ethical principles. The REBs were also willing for us to publish the times required for REB approval for different studies compared with the time taken for approval of more traditional trial methodologies [12, 14].

As the integrated oral consent process is a major change from conventional methodologies, we have established processes for Site Initiation Visits (SIVs) to inform all staff investigators that not only is oral consent ethical, but also that, with practice, it can be wholly integrated with the usual conversations with patients and their families. We provide templates of typical discussions we have with patients and emphasize the details that must be recorded in the EMRs, which become a source document. We have surveyed patients to evaluate their experience with the ICM. The results were highly positive, with over 90% of patients being satisfied by the entire process for both explaining the clinical trial and answering their questions [12].

Efficient REB review

Regulatory delays are a significant and well-described source of frustration, increased cost, and delays in opening clinical trials [36]. Our team has had an ongoing constructive dialogue with both local and provincial REBs and Health Canada. These lines of communication start early in the process of designing a trial. All these organizations want clinical trials to take place, but we all want them to be safe, meaningful and compliant with various regulatory requirements. This two-way dialogue has been highly effective, and has at times resulted in protocol changes that have allowed the trial to proceed with a modified design (e.g., REaCT-TAPS) [37].

The major challenge has been the need to present the concept of the ICM to each new REB. We have tried to overcome this by using centralized REB (e.g., OCREB in Ontario) for all trials when possible. OCREB has been very supportive and have created a series of REaCT-specific templates to facilitate the review process.

Web-based randomization in the clinic

Traditionally after a detailed discussion regarding informed consent, a study-specific CRA will randomize a patient after various study-designated tests and eligibility confirmation by the investigator have been completed. This process can lead to delays for the patient before they can receive their study treatment. For most REaCT trials, randomization has been performed using a web-based application after study consent has been given. This means the patient is often aware of what study arm they are on before they leave the clinic. REaCT trials do not require any additional investigations or clinic visits beyond the standard of care, and this has likely helped accrual.

Real-time data capture and management

A significant challenge for many trials is the requirement for data capture from multiple sources, being transcribed onto case report forms (CRFs) and then entered into electronic databases. A simple example is biochemistry results that are generated on electronic EMRs, then copied onto paper CRFs, and then re-entered into a database. All steps are adding expense and increase the potential for errors. We have had success in collecting patient data in a timely fashion by sending computer-generated email templates to physicians timed with patients visit to obtain relevant trial-related outcomes. Our next step will be to explore how we can capture and manage this data electronically in real-time.

Regular team communication, internal auditing, and monitoring

Every 6–8 weeks a trial oversight meeting occurs where patient and staff concerns and accrual rates are discussed. These meetings allow the CRAs, managers, and clinical investigators to address issues quickly and efficiently regarding trial conduct. Following this meeting, all investigators

are sent an email informing them about accrual, reminding them of eligibility criteria, and listing successes and challenges that particular studies are facing. All REaCT trials are monitored (either peer-monitored or by the sponsor institution). Due to the low-risk nature of most REaCT trials, monitoring is typically done on the first 1–2 patients, at the trial midpoint and when the trial is approaching its target accrual.

Economic evaluations

Most REaCT trials incorporate embedded economic evaluations into the protocol. We feel these analyses add considerably to the REaCT program, as all healthcare systems globally are looking at ways of controlling spiraling healthcare costs, while at the same time improving the quality of care patients receive. Trials such as REaCT-TC, which is comparing G-CSF use (drug costs > $4,000) with ciprofloxacin (drug costs $50) as primary febrile neutropenia prophylaxis in patients receiving TC chemotherapy for breast cancer, could potentially save patients and the healthcare system millions of dollars a year if equivalence is shown. To ensure that the results of the REaCT-based economic evaluations are relevant to clinical and policy decision-making, we use a range of comparators. These include measures of health-related preference weights to enable quality-adjusted life year calculations. We also try and study populations and interventions that match the full spectrum of everyday clinical settings in order to maximize applicability and generalizability [38]. The major challenge with economic evaluations is that they involve patients completing more questionnaires to obtain economic and health utility data, which can be inconvenient for them and adds to the workload of the research staff to ensure they are completed and data entered. However, to date, patients remain very supportive in these endeavors.

Knowledge mobilization activities

Unfortunately, simply performing research does not automatically translate into improved patient care and treatment [39]. The REaCT program has built-in implementation strategies for engaging key stakeholders such as decision makers and end users (e.g., physicians and patients) before any protocol is undertaken, in order to ensure rapid dissemination and implementation of results. The REaCT team consists of knowledge translation and mobilization experts who also hold positions in provincial and national healthcare policy organizations in Canada. Hopefully, with the complete accrual of several trials we will see changes in practice that impact on not only physician behavior but also clinical outcomes of patients.

Discussion

The challenges of opening and performing clinical trials are well recognized, and it is likely a combination of reasons that contribute to many clinical trials never getting off the ground, or failing to meet their recruitment goal, resulting in early trial termination or inconclusive results [8]. The recognition of these barriers has led to a broad range of potential strategies to improve accessibility to oncology trials. The REaCT program was created to improve care and outcomes for cancer patients. While this model is not a panacea and certainly not a substitute for well-designed phase 1, 2, and 3 trials, it has been a remarkable success considering its very limited funding. We have identified major barriers to clinical trial participation, and recognized and demonstrated ways to overcome some of these barriers using practical means. To date, these have focused on designing trials with practical yet clinically relevant endpoints, avoidance of superfluous data collection, implementation of integrated oral consent processes, and minimizing the need for patients to return to hospital for extra clinic visits.

Impact thus far: In close to 4 years, 15 different trials are ongoing or completed, enrolling over 2000 participants. Surveys of patients have shown great popularity with the oral consent model. With the completion of accrual of the REaCT-BTA and REaCT-G studies, we are optimistic that we will be able to make a significant difference to the treatment of cancer patients globally. We have also hopefully learned from our mistakes, for example, the REaCT-TN trial was a pilot study evaluating different adjuvant chemotherapy regimens for triple-negative breast cancer. Despite the initial enthusiasm from investigators, accrual rates were too low for a definitive efficacy trial to be performed.

In the future, we hope to improve data collection and possibly avoid paper CRFs by using ‘big data’ for data collection. We are also continually striving to expand to other sites and invigorate young physicians and researchers so that they will want to be contributors and leaders of all types of clinical research in the future.

In conclusion, there will always be clinical questions that need answering. We hope that the REaCT Program will provide a platform for a new generation of researchers to lead trials that directly affect our patients. To answer these clinically relevant questions, we need pragmatic trials that integrate simple trial designs and innovative processes, allowing trials to run at lower costs with greater patient accessibility.

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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 to disclose (Basulaiman, Fergusson, Vandermeer, Arnaout, Hilton, Joy, Robinson, Califaretti, Stober, Sienkiewicz, Thavorn, 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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