BMJ Open

Prospective randomised controlled trial using the REthinking Clinical Trials (REaCT) platform and National Surgical Quality Improvement Program (NSQIP) to compare no preparation versus preoperative oral antibiotics alone for surgical site infection rates in elective colon surgery: a protocol

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To cite: Apte SS, Moloo H, Jeong A, *et al*. Prospective randomised controlled trial using the REthinking Clinical Trials (REaCT) platform and National Surgical Quality Improvement Program (NSQIP) to compare no preparation versus preoperative oral antibiotics alone for surgical site infection rates in elective colon surgery: a protocol. *BMJ Open* 2020;**10**:e036866. doi:10.1136/bmjopen-2020-036866

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-036866).

Received 08 January 2020
Revised 24 April 2020
Accepted 02 June 2020

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ABSTRACT

Introduction Despite 40 randomised controlled trials (RCTs) investigating preoperative oral antibiotics (OA) and mechanical bowel preparation (MBP) to reduce surgical site infection (SSI) rate following colon surgery, there has *never* been an RCT published comparing OA alone versus no preparation. Of the four possible regimens (OA alone, MBP alone, OA plus MBP and no preparation), randomised evidence is conflicting for studied groups. Furthermore, guidelines vary, with recommendations for OA alone, OA plus MBP or no preparation. The National Surgical Quality Improvement Program (NSQIP) has automated data collection for surgical patients. Similarly, the 'REthinking Clinical Trials' (REaCT) platform increases RCT enrolment by simplifying pragmatic trial design. In this novel RCT protocol, we combine REaCT and NSQIP to compare OA alone versus no preparation for SSI rate reduction in elective colon surgery. To our knowledge, this is the first published RCT protocol that leverages NSQIP for data collection. In our feasibility study, 67 of 74 eligible patients (90%) were enrolled and 63 of 67 (94%) were adherent to protocol. The 'REaCT–NSQIP' trial design has great potential to efficiently generate level I evidence for other perioperative interventions.

Methods and analysis SSI rates following elective colorectal surgery after preoperative OA or no preparation will be compared. We predict 45% relative rate reduction of SSI, improvement in length of stay, reduced costs and increased quality of life, with similar antibiotic-related complications. Consent, using the 'integrated consent model', and randomisation on a mobile device are completed by the surgeon in a single clinical encounter. Data collection for the primary end point is automatic through NSQIP. Analysis of cost per weighted case, cost utility and quality-adjusted life years will be done.

Ethics and dissemination This study is approved by The Ontario Cancer Research Ethics Board. Results will be disseminated in surgical conferences and peer-reviewed journals.

Trial registration number NCT03663504; Pre-results, recruitment phase.

Strengths and limitations of this study

- The intervention groups in this randomised controlled trial (oral antibiotics (OA) alone and no preparation) have never been directly compared in a prospective, randomised trial.
- The REthinking Clinical Trials (REaCT) design with integrated oral consent and web-based randomisation dramatically improves enrolment of eligible patients.
- The use of validated and established automatic data collection methods via National Surgical Quality Improvement Program (NSQIP) maximises trial efficiency and reduces cost.
- Only two standard-of-care perioperative interventions, for which there is clinical equipoise, can be compared in the REaCT–NSQIP trial design.
- The number of eligible patients limits the study power necessary to perform a three-arm trial of OA plus mechanical bowel preparation, OA alone and no preparation—interventions not directly compared in historical trials.

INTRODUCTION

Surgical site infections after elective colon surgery are frequent, serious and costly.

Approximately 20% of patients undergoing colorectal surgery will suffer from surgical site infection (SSI).[1 2] SSIs are associated with significant morbidity, 7–10 days increased length of stay (LOS),[3] twofold to threefold higher healthcare costs[3–5] and mortality.[6] In addition to standard-of-care intravenous antibiotic (IVA) prophylaxis, there are four possible bowel preparation regimens for SSI prevention prior to colorectal surgery: (1) oral antibiotics (OA) alone, (2) mechanical bowel preparation (MBP) alone, (3) OA plus MBP and (4) no preparation. In previous studies, OA includes three doses of oral neomycin and metronidazole given the day before surgery.[7–9] MBP commonly refers to either oral polyethylene glycol or sodium phosphate solution to cleanse the entire colon.[10–13] Both interventions are aimed at reducing the faecal bacterial load, theoretically preventing SSI after colon resection.

Despite over 40 randomised controlled trials (RCTs), there is still clinical equipoise regarding the optimal preoperative bowel preparation regimen to prevent SSI after colon surgery. For example, The American Society of Colon and Rectal Surgeons,[14] WHO[15] and American College of Surgeons[16] recommend OA plus MBP. The WHO cites an absence of randomised evidence regarding the use of OA alone, while the American College of Surgeons does not recommend OA alone. Additionally, the Canadian Society of Colorectal Surgeons[17] and the UK National Institute for Health and Care Excellence[18] recommend against the use of MBP, without specific mention of the role of OA.

Historically, the use of MBP prior to colon surgery was common. This rationale was based on consensus opinion assuming an association between reducing faecal bacterial load and the incidence of SSI.[19–21] Since that time, a series of retrospective studies, followed by RCTs questioned the benefit of MBP. At present, a total of 13 published RCTs,[10 12 13 22–31] 8 meta-analyses[32–39] and a Cochrane review[40] have confirmed that there is no statistically significant evidence that elective colon surgery patients benefit from preoperative MBP alone, and in fact MBP may be associated with an increased SSI rate.[25 30] Furthermore, MBP is associated with significant side effects, including abdominal pain and bloating (12%–22%),[41] electrolyte disturbances (28%)[42 43] and dehydration, particularly in patients greater than 60 years old,[44] which is the median age of elective colon surgery patients.[45]

During the same time period, OA were added to MBP in an effort to further reduce the faecal bacterial load. In the 1970s, Clarke and colleagues completed a series of clinical trials comparing MBP plus or minus OA versus MBP plus IV antibiotics, concluding OA to be important in SSI prevention.[19 46–48] In 1969, Polk *et al* published a landmark paper showing the benefit of IV antibiotic prophylaxis in intestinal surgery,[49] a finding that has been extensively replicated.[50] Thereafter, OA fell out of favour, replaced by IVA, despite an absence of high-quality randomised evidence to support the elimination of OA from the preoperative regimen.[9]

More recently, there has been a resurgence of interest in OA to reduce SSI incidence after colon surgery. For instance, three meta-analyses of 7, 11 and 14 RCTs, respectively, demonstrated a reduction in SSI rate of approximately 45% with the use of OA plus MBP as compared with MBP alone.[51–53] Additionally, a recent network meta-analysis of relevant RCTs has also suggested an SSI rate reduction for OA plus MBP as compared with MBP alone. In the absence of direct RCT comparisons, this meta-analysis suggests a reduced rate of SSI for the OA group as compared with no preparation, and possible equivalence of the OA and OA plus MBP groups.[54] Remarkably, of the four possible bowel preparation regimens aimed at reducing SSI rate before colon surgery, there has *never* been an RCT published comparing OA alone with no preparation. Furthermore, there is only a single, recent RCT comparing OA plus MBP with no preparation, which reported no significant difference in SSI rate.[7] This highlights a significant gap in the level I evidence comparing OA alone or OA plus MBP versus no preparation for SSI prevention after colon surgery. Retrospectively, two large studies from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) (>30 000 patients) and one large meta-analysis of prospective studies (69 000 patients) have confirmed that many centres are using OA alone as a standard of care for colorectal surgery patients.[45 55 56] These studies suggested that OA alone is associated with similar SSI rates to OA plus MBP, and lower SSI rates as compared with both MBP alone and no preparation. Additionally, the rate of antibiotic resistance or *Clostridium difficile* infection is similar between the OA alone, no preparation and OA plus MBP groups.[57] It is important to note that in all relevant studies, appropriate IVA prophylaxis was administered, and this continues to be the standard practice for all patients.

To summarise the randomised evidence: (1) no preparation is favoured to MBP alone and (2) OA plus MBP is favoured to MBP alone. Based on this, and the retrospective evidence that OA containing regimens yield lower SSI rates versus no preparation, some experts have advocated for a shift in practice from no preparation to OA alone, ostensibly reducing SSI rates, while avoiding the side effects of MBP.

This is a provocative hypothesis without supporting randomised evidence which warrants evaluation in a well-designed RCT. The trial protocol reported here will fill that crucial knowledge gap.

REthinking Clinical Trials (REaCT) is a streamlined pragmatic trial platform designed to address falling numbers in clinical trial enrolment.[58] In Canada, less than 5.8% of eligible cancer patients are enrolled in clinical trials.[59] Aimed at comparing two standard-of-care interventions for which there is known clinical equipoise, the REaCT platform streamlines trial conduct using an 'integrated consent model', practical data capture and web-based randomisation.[60] First conceptualised at The Ottawa Hospital, the REaCT programme has been

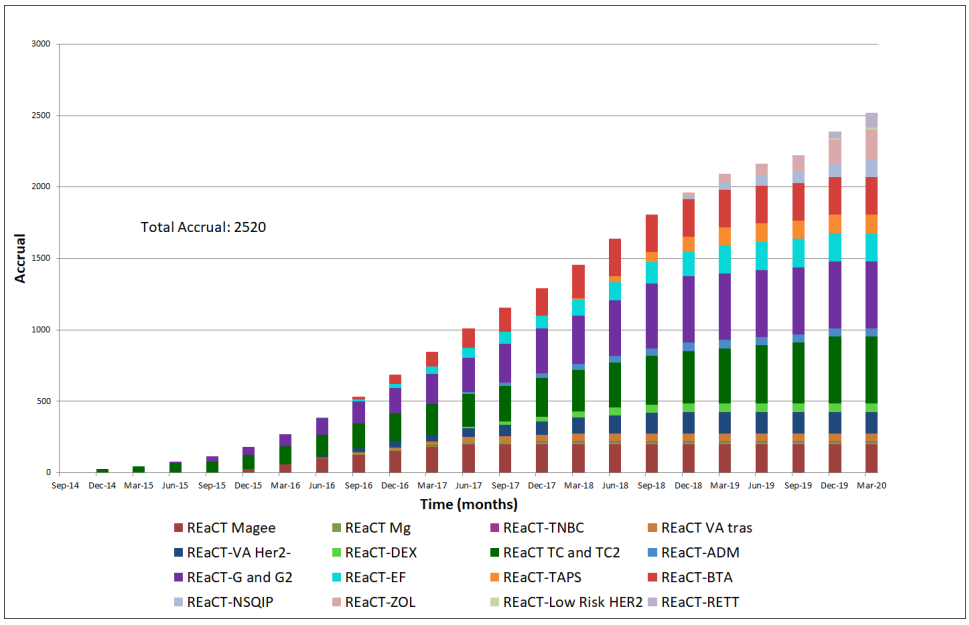

Figure 1 The REaCT platform has been highly successful over the past 5 years, with 15 completed or ongoing pragmatic trials and over 2500 patients enrolled to date (April 2020). NSQIP, National Surgical Quality Improvement Program; REaCT, REthinking Clinical Trials.

highly successful at overcoming regulatory and financial barriers—to date there are over 15 ongoing REaCT studies, with >2500 patients randomised in just 5 years[61] (figure 1). On average, ≈80% of eligible patients participate in REaCT, far above the enrolment rates for eligible cancer patients in Canada.[59] Given the clinical equipoise between the two standard-of-care interventions (OA alone vs no preparation) compared in this trial, the REaCT platform is well suited to investigate this perioperative intervention.

Standardised quality improvement infrastructure such as NSQIP and Enhanced Recovery After Surgery (ERAS) have become integral to perioperative care. ERAS is a widely adopted, multimodal programme of perioperative interventions, supported by level I evidence.[62 63] These interventions can accelerate recovery, decrease complications and result in earlier discharge. Often, the quality metrics and outcomes of the ERAS programme are measured through data collected as part of the NSQIP.[64] NSQIP is the leading, validated, risk-adjusted outcome measurement programme aimed at improving the quality of surgical care in North America.[65] Using trained surgical clinical reviewers (SCRs), NSQIP centres collect perioperative data from the medical record, including clinical variables, procedure data and 30-day outcomes. Currently, more than 600 hospitals in the world and 47 Ontario hospitals participate in NSQIP.[65–67] Infrastructure such as NSQIP and ERAS present an opportunity to collect data not only for quality improvement initiatives, but also for perioperative pragmatic trials. In this novel REaCT–NSQIP trial design, we have leveraged the ease and rigour of real-time data collection through NSQIP and combined it with the streamlined trial methodology of REaCT. To our knowledge, this is the first published RCT protocol to have used NSQIP in this fashion. The REaCT–NSQIP design could easily be adopted at other centres as an efficient way to generate level I evidence for other perioperative quality improvement strategies.

Our institution has completed a single-centred feasibility study from October 2018 to June 2019 with a primary end point of >80% enrolment and >80% adherence to treatment for eligible patients. Secondary end points include >90% automatic NSQIP data capture and <5% loss to follow-up. Over the 8-month period, the study demonstrated remarkable enrolment of 67 of 74 eligible patients (90%). Only four patients were non-compliant (94% protocol compliance) (figure 2). There were zero losses to follow-up for the primary end point. NSQIP automatic data capture was successful 100% of the time. Having exceeded our benchmark for feasibility, we have undertaken a multicentre trial at four other high-volume hospitals. In this novel, multicentre, pragmatic RCT, we will compare SSI rates in elective colon surgery patients for preoperative OA alone versus no preparation. By combining the REaCT platform with automatic NSQIP data collection, the REaCT–NSQIP protocol is a model for randomised trial efficiency (figure 3). The successful completion of this trial will highlight the potential for the REaCT–NSQIP design to improve the value and quality of surgical care by efficiently generating level I evidence for other perioperative interventions.

METHODS AND ANALYSIS

Study design

The REaCT–NSQIP trial is a multicentre, prospective, single-blinded, pragmatic RCT comparing OA alone versus no preparation for surgical site infection rates

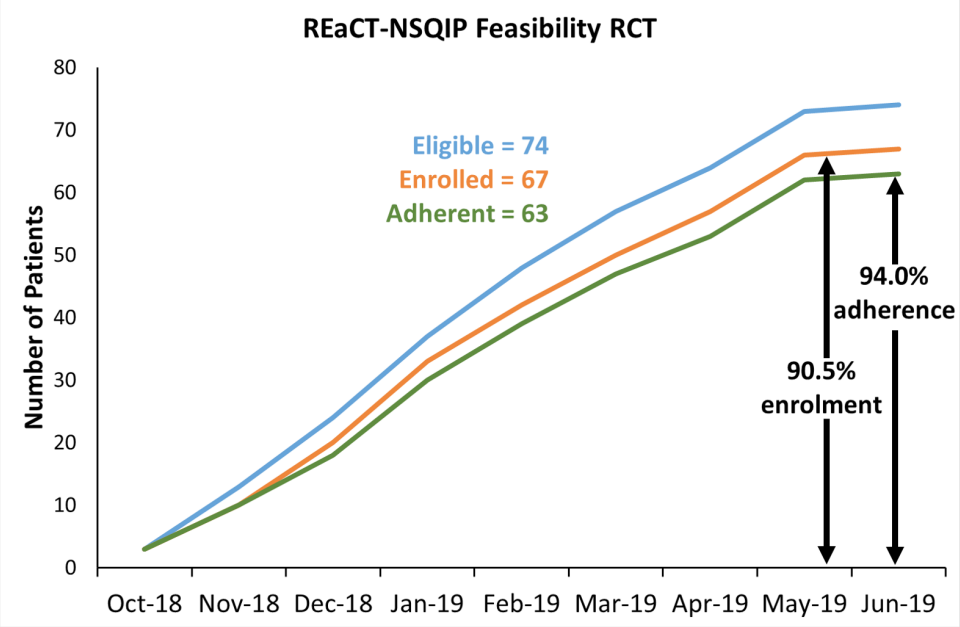

Figure 2 Cumulative total of eligible versus enrolled patients in the 8-month, single centred, REaCT–NSQIP feasibility trial. In our pilot feasibility trial at The Ottawa Hospital, we enrolled 67 patients over 8 months, out of a total of 74 eligible patients (>90% enrolment rate). Adherence to preoperative OA as per protocol was 94%. NSQIP, National Surgical Quality Improvement Program; OA, oral antibiotics; RCT, randomised controlled trial; REaCT, REthinking Clinical Trials.

in elective colon surgery. The novel REaCT–NSQIP design embeds the research question in clinical practice, controlling only the studied intervention, increasing the generalisability of the trial results.

Intervention

Patients will be randomised to either:
ARM A—no preparation
or
ARM B—OA alone; neomycin and metronidazole, 1 g of each, administered at 13:00, 15:00 and 20:00 hours the day before surgery.

Both arms will receive pre-incision IVA prophylaxis according to the standard of care at the treating centre. Neither arm will receive a MBP.

Hypothesis

The use of OA alone compared with no preparation will result in a 45% relative risk reduction of SSI, with an associated decrease in postoperative LOS, hospital costs and increased patient quality of life (QoL), with no increase in antibiotic-related adverse events.

Study population

All patients 18 years or older undergoing elective colon resection (partial or total colectomy with or without anastomosis, or abdominal perineal resection) at participating NSQIP centres will be eligible for enrolment. Patients will be excluded if they cannot provide oral consent; OAs are contraindicated (ie, adverse or allergic reaction); an active infection requiring antibiotics is present; there is a requirement for MBP (rectal resection with anastomosis, transanal excision, intraoperative colonoscopy or surgeon discretion) or they are undergoing emergency colon surgery with no opportunity to administer OA the day before surgery.

Screening, consent and randomisation

Patients will be screened, consented and randomised using the REaCT platform during the clinical encounter when consent for surgery is obtained. Informed consent for trial participation will be verbally obtained by the surgical team (online supplementary appendix 1) and documented directly in the medical record as part of the visit note (online supplementary appendix 2). The patient is then given a copy of the consent template. This method of oral trial consent is called the integrated consent model and is one of the hallmarks of the REaCT platform. Importantly, the integrated consent model negates the need for separate points of contact to enrol and randomise patients. Site-stratified, permuted-block randomisation of eligible and consented patients is done in real time, in the clinic, through a secure, web-based interface on the surgeon's or REaCT coordinator's mobile device. Through a web-based checklist on the REaCT interface, eligibility criteria are ensured, a study ID is automatically generated and the patient is administratively enrolled. Randomisation and group allocation occur immediately. Patients in the OA arm receive a prescription and instructions on administration of preoperative OAs.

Study outcomes and data collection

Primary outcome

The primary outcome of this study is a reduction in SSI rate at 30 days postoperatively (the time frame for perioperative data collection through NSQIP).

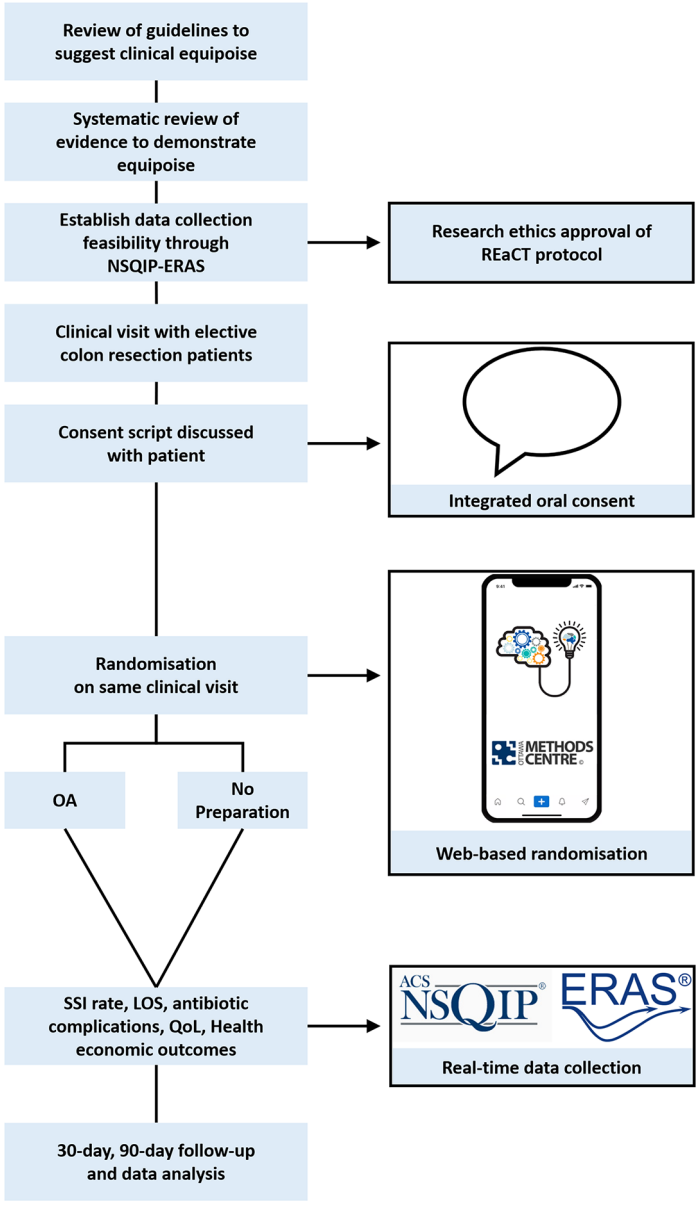

Figure 3 REaCT–NSQIP trial enrolment flow chart highlighting the integrated oral consent, web-based randomisation and automatic data collection through NSQIP–ERAS. *Adapted from Hilton *et al*[58]. ERAS, Enhanced Recovery After Surgery; LOS, length of stay; NSQIP, National Surgical Quality Improvement Program; QoL, quality of life; REaCT, REthinking Clinical Trials; SSI, surgical site infection.

Secondary outcomes

The secondary outcomes of this study are LOS, incidence of *C. difficile* infection at 90 days, antibiotic-resistant infectious complications at 30 days, QoL, incremental cost-effectiveness ratio and incidence of subgroup infectious complications at 30 days (deep SSI, superficial SSI, organ space SSI, anastomotic leak and non-SSIs).

The primary and secondary outcomes, as well as all other relevant clinical variables will be extracted from the NSQIP-linked clinical or administrative chart by trained, blinded SCRs at NSQIP centres. These data are collected automatically regardless of trial enrolment, as a part of NSQIP. Secondary outcomes not collected by NSQIP will be retrieved from the clinical chart via a custom algorithm and linked to the NSQIP data. Patient compliance with OA and determination of antibiotic-related side effects will be ascertained by a clinical research assistant (CRA). To minimise bias, patients in both groups will be asked open-ended questions by telephone regarding symptoms on the day before surgery. The patient reported QoL, measured using the SF-36 and EQ-5D-5L questionnaire at baseline and at 30 days postoperatively, will also be collected by a CRA.[68 69] In keeping with the pragmatic nature of the study, trial follow-up will be no different than standard surgical follow-up that occurs at 4–6 weeks.

Data analysis

The data analysis will be undertaken by the Ottawa Methods Centre. A report will also be generated after

enrolment of 100 patients each to be reviewed by the Data Safety Monitoring Board (DSMB).

Projected reduction in SSI rate and sample size calculation

Based on the published data, we estimate a 45% relative reduction in SSI rates with preoperative OA alone as compared with the no preparation group.[45 51–53 57 70] With the NSQIP Ontario Collaborative (NSQIP-ON) SSI rate for colorectal patients at 13%,[64] a sample size of 828 patients (414 patients per arm) provides 80% power to detect a 45% relative risk reduction (two-sided α 5%). Given the >99% 30-day follow-up rate of colorectal cases in Ontario NSQIP centres in 2016–2017, we expect <5% loss to follow-up.

The sample size will be reassessed at ½ trial accrual using the NSQIP-ON Collaborative SSI rate, thereby avoiding an interim analysis. NSQIP-ON is a group of >40 hospitals in Ontario, Canada which collect data via NSQIP and publish yearly reports of quality improvement metrics including SSI rate for colon surgery. Centres participating in the REaCT–NSQIP multicentre trial are members of NSQIP-ON. Consequently, the NSQIP-ON SSI rate is taken from a significantly larger patient population, which includes, but is not limited to, the sample of patients participating in the REaCT–NSQIP trial.

Reduction in LOS

Given the current sample size, based on a mean LOS of 7.2 days (SD 5.0),[64] this study has an >80% power to detect an absolute decrease of 1.0 days in mean LOS.

Patient-reported QoL

The SF-36 has been validated as a measure of postoperative recovery in patients undergoing colorectal surgery.[69 71] The EQ-5D-5L allows direct estimation of health utility values.[68 72] Baseline and postoperative scores will be compared using the standardised response means, and the magnitude of the postoperative change will be considered in relation to the minimal clinically important difference, which represents the smallest change that would influence patient management.[73 74]

C. difficile and antibiotic resistance complications

NSQIP data will be linked to postoperative *C. difficile,* antibiotic sensitivity results and antibiotic resistance complications and these will be directly compared between the two study arms.

Descriptive analysis

Baseline characteristics of each treatment group will be presented as means (continuous measures) or proportions (categorical or ordinal data) with 95% CIs.

Intention-to-treat analysis

All statistical analyses will be done in an intention-to-treat fashion, based on all subjects who underwent randomisation. Additionally, a per-protocol analysis of the primary and secondary outcomes based on treatment received will be conducted.

Analysis of primary outcomes

The primary outcome (incidence of SSI) will be measured dichotomously as a combination of deep and superficial SSI. The risk difference will be calculated with a 95% CI.

Analysis of secondary outcomes

Relative risk and mean differences will be calculated and presented with 95% CIs. This will include a subgroup analysis of deep, superficial, organ space and non-SSI rates if event number allows.

Health economic analysis

Using individual case costing, we will compare the total cost per weighted case between the groups. Given that the fiscal year 2015/2016 mean total cost per weighted case at our local centre was $C7133 (SD $C636) and case weight 2.75, we have >90% power to detect a cost saving of $C190 per weighted case ($C522 per patient). A cost-utility analysis will be also conducted from a perspective of the publicly funded healthcare system. Specifically, the costs and health outcomes including the number of SSI cases prevented and quality-adjusted life years (QALYs) will be compared. Analysis will incorporate data on efficacy, resource use and patients' utility values up to 3 months postsurgery. QALYs will be estimated for each patient within the clinical trial using the total area under the curve method.[75 76] The incremental cost and QALYs gained will be estimated using regression analysis. Uncertainty in the analysis will be addressed by estimating 95% CIs using a non-parametric bootstrapping method. Results from bootstrapping will also be used to depict cost-effectiveness acceptability curves, which link the probability of the intervention being cost-effective over a range of potential threshold values (λ) that the health system may be willing to pay for an additional unit of effect. The cost-effectiveness analysis will adhere to the best practices for conducting and reporting of health economic evaluations.[77]

Compliance and loss to follow-up

Secondary analyses will be considered to understand the influence of compliance and losses to follow-up on the robustness of the intention-to-treat analysis. In general, a per-protocol analysis of primary and secondary outcomes will be performed and compared with the intention-to-treat analysis. Due to the pragmatic nature of the REaCT–NSQIP trial, the aim of this study is assessing utility of the intervention in a real-world setting. Consequently, it is imperative that methods to improve compliance not be specific to the clinical trial setting (eg, a CRA phone call reminder that would happen only within the context of the trial, but not during routine clinical care). The trial does, however, use information sheets similar to teaching brochures that are commonly provided to patients as part of routine surgical care.

Data storage, custodianship and availability

Data will be anonymised with study ID, stored, encrypted and password-protected at The Ottawa Hospital Research Institute, REaCT section. It will be accessible to the

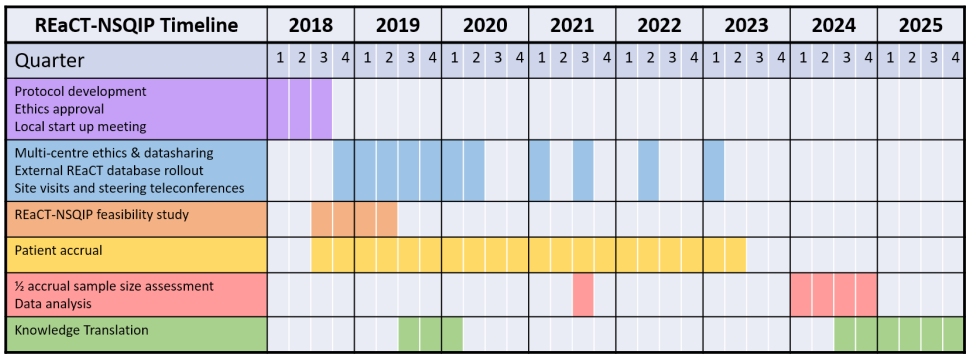

Figure 4 The REaCT–NSQIP single-centred feasibility study was completed in Q2 2019. Given that the statistical power of the study is dependent on the baseline SSI rate across participating sites, the SSI rate of the NSQIP-ON Collaborative (which includes >40 hospitals in the trial region of Ontario) will be reassessed at the midpoint of trial enrolment (≈Q3 2021), allowing for adjustment of the final sample size. NSQIP, National Surgical Quality Improvement Program; REaCT, REthinking Clinical Trials; SSI, surgical site infection.

Ottawa Methods Centre, the DSMB and study authors involved in data interpretation, analysis and knowledge translation. Raw, anonymised data will be kept for a total of 10 years. Any data with identifying information will be securely destroyed 1 year after study completion. Technical appendix, statistical code and data set will be available by specific request through The Ottawa Hospital Research Institute and Ottawa Methods Centre (Trial: OTT18-03 REaCT–NSQIP, methodscentre@toh.ca).

Study timeline

Enrolment

Four external participating high-volume Ontario hospitals have completed site administrative enrolment in the REaCT–NSQIP study reported here. Enrolment of patients at external sites is anticipated in 2020. Given that current enrolment at the primary site is 130 patients, and projected external site enrolment ranges from 50 to 100 patients/year, we anticipate full trial enrolment (828 patients) in 2023 (figure 4).

Analysis, interpretation and knowledge translation

Data extraction, transfer, cleaning and locking and analysis will begin 4 months after the last patient undergoes surgical intervention, allowing for 30-day and 90-day follow-up. Analysis by The Ottawa Methods Centre (primary and secondary outcomes) and the Ottawa Hospital Research Institute (economic and QoL outcomes) will be completed thereafter. Interpretation, knowledge translation and publication will be completed by 2024.

REaCT–NSQIP trial steering committee

The REaCT–NSQIP Trial Steering Committee consists of the principal investigator, co-investigators, colorectal surgeons, a statistician and patient with lived experience. This body has international experts in perioperative trial design, clinical trials, the REaCT platform, statistical analysis and methodology, NSQIP, colorectal surgery, infectious diseases and economic analysis. The steering committee will oversee adherence to the protocol and monitor trial progress, safety and protocol amendments. Persons who attend committee meetings, but do not vote, include the REaCT CRAs. The committee will meet under the following circumstances: (1) at trial start-up, quarterly via teleconference, (2) at external site initiation and (3) if unforeseen problems arise affecting trial progress. The trial sponsor (The Ottawa Hospital Research Institute) will oversee the DSMB, which is independent of trial investigators. This board will consist of internal and external reviewers, facilitated by the trial sponsor.

Patient and public involvement

This protocol is based on the REaCT pragmatic trial design. The REaCT methodology addresses clinical questions for which there is equipoise identified by both the treating physicians and the participating patient population. The conduct of this study, including the usage of the integrated consent model, was developed in conjunction with patient stakeholders. Moreover, REaCT is focused on selecting outcomes that have demonstrated value to patients.[58] In the current study, the primary outcome measure (SSI rate) is a quality improvement target identified by Health Quality Ontario (HQO) (https://www.hqontario.ca). HQO is a provincial advisor on health quality issues which directly involves patients in its leadership, mandate, structure and strategic plan. Furthermore, clinical outcomes and QoL measures will be reported to HQO, highlighting the patient experience in this study.

ETHICS AND DISSEMINATION

This study was approved by The Ontario Cancer Research Ethics Board (OCREB) on 14 May 2018 (Ethics ID: CTO 1481). Any necessary protocol amendments will be made formally in conjunction with the trial sponsor, OCREB and clinical trial registries (clinicaltrials.gov). The results of this trial will be disseminated through oral and poster presentations at international surgical conferences. At least two publications in peer-reviewed journals will be authored, focusing on the clinical, economic and

QoL outcomes. Results will also be discussed at quality improvement meetings of relevant stakeholders such as the Ontario Surgical Quality Improvement Network, Health Quality Ontario and the Canadian Association of General Surgeons Clinical Practice Committee.

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Acknowledgements The authors would like to acknowledge Deanna Rothwell of Performance Measurement at The Ottawa Hospital, The Ottawa Methods Centre for statistical and methods assistance, The Ottawa Hospital Clinical Care leads for colorectal and surgical oncology, and our other collaborating sites: Dr Joel Weaver—The Queensway Carleton Hospital (Ottawa, ON), Dr Mantaj Brar—Mount Sinai Hospital (Toronto, ON), Dr Sami Chadi—Toronto Western Hospital (Toronto, ON) and Dr Usmaan Hameed—North York General Hospital (Toronto, ON).

Contributors SSA is a clinical surgical fellow and co-investigator who wrote the manuscript, is responsible for the trial protocol, trial coordination, data analysis, interpretation and knowledge translation. HM is a surgeon and co-investigator who helped with trial conceptualisation and protocol design and is responsible for data analysis and interpretation. AJ is a research coordinator who helped write the manuscript and is responsible for trial progress, daily trial management and data analysis. ML and LV are research coordinators who are responsible for trial coordination and initiation. KS is a clinician investigator and infectious diseases expert who helped with protocol design and is responsible for data analysis and interpretation. KT is a clinical epidemiologist who helped with protocol design and is responsible for the health economic analysis and data interpretation. DAF is a clinical epidemiologist and REaCT expert who helped with protocol design and is responsible for the statistical plan, data analysis and interpretation. MC is an oncologist, clinician investigator and REaCT expert who helped with protocol design and is responsible for data analysis and interpretation. RCA is the principal investigator and corresponding author who conceptualised the study, designed the study protocol, wrote the manuscript and coordinated the trial and is responsible for data analysis, interpretation and knowledge translation.

Funding Health Sciences Centres of Ontario. The trial sponsor and funding sources have no role or ultimate authority in study design: collection, management, analysis, data interpretation, manuscript writing or decision to submit the manuscript for publication.

Competing interests RCA, SSA, HM, AJ, KS and KT do not have any conflicts of interests to disclose. DAF is a senior scientist at Ottawa Methods Centre. DAF and MC are the founders and leads of the Ottawa REaCT study platform.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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