OPPORTUNITIES TO IMPROVE ACCRUAL TO SURGICAL CLINICAL TRIALS

FACTORS AFFECTING RECRUITMENT TO SURGICAL ONCOLOGY CLINICAL TRIALS AND OPPORTUNITIES TO IMPROVE ACCRUAL

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LAY ABSTRACT

The most common factor that leads to trial failure is poor recruitment. A trial is a prospective study of an intervention (either with a comparator or not). This thesis discusses issues with recruitment and ways to improve recruitment. It uses a series of trials. The first trial investigated nutritional supplements before surgery. Problems with recruitment were related to the short time interval before surgery and the opportunity for improvement is to approach participants during their first appointment with surgeons.

The second trial investigated the feasibility of performing a surgical intervention in patients with colon cancer and liver metastases, in which the liver and colon are removed at the same time. A method of using provincial databases to identify potential participants is proposed.

Next, the thesis proposes a surgical trial of a surgical technique using the methods from the previous studies and ends with the lessons learned from the thesis.

ABSTRACT

Surgical trials involve patients undergoing a surgical intervention. Poor recruitment is the most important issue that can lead to study failure.

Chapter 1 provides the conceptual framework of recruitment issues that can arise when conducting a surgical trial. Different methodological challenges that lead to poor recruitment are discussed based on the different steps of a trial. It provides a rationale for conducting the included studies.

Chapter 2 describes a double blind, placebo controlled randomized clinical trial; a pilot feasibility trial evaluating the use of perioperative nutritional supplements versus placebo for patients undergoing gastrointestinal cancer surgery. This chapter expands on issues related to recruitment to surgical trials in this setting (i.e., surgical trials that compare a medical intervention or drug among patients undergoing surgery) and explores potential opportunities to improve accrual.

Chapter 3 presents a single arm, multi-institutional, pilot trial, evaluating the feasibility of enrolling patients to a trial involving an innovative surgical intervention. This chapter evaluates recruitment issues to surgical trials that investigate surgical interventions and explores potential solutions to these challenges.

Chapter 4 reports on a prospective study that was performed alongside the trial presented in Chapter 3 that evaluated the use of population-based electronic databases as a possible opportunity to improve accrual.

Chapter 5 describes a protocol for a randomized controlled trial comparing simultaneous versus staged resection for synchronous colorectal cancer liver metastases. It uses the

results gathered from previous trials for its design and proposes the use of population-based databases as a recruitment strategy.

Chapter 6 discusses the lessons learned from the two different trials and the one prospective cohort study as a form of conclusion, examining possible opportunities to improve recruitment, based on the challenges described in this PhD thesis. This chapter also discusses limitations as well as future research planned based on this thesis work.

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COVID-19 IMPACT STATEMENT

In March 2020, due to government mandated changes to research activity related to the COVID-19 pandemic, the steering committee of the trial presented in Chapter 2 (Perioperative Optimization with Nutritional Supplements in Patients Undergoing Gastrointestinal Surgery for Cancer" or "PROGRESS") performed an interim blinded data analysis of the primary outcome (enrollment fraction) and decided, based on the available results, the stable trajectory of enrollment rate throughout the trial, and assuming the same trend of enrollment would continue, that a larger sample size would not be able to show a higher enrollment rate and therefore, it would not change the results of the trial. Therefore, given the inabilities of following trial procedures during the pandemic, and the perceived small impact on trial outcome, it was decided to stop the trial early with the sample size of 71 (planned 100).

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LIST OF ABBREVIATION

ACCESS	Population-based Accrual to the simultaneous resection of Colorectal Cancer with Synchronous liver metastases Study
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CCI	Comprehensive Complication Index
CD	Clavien-Dindo Classification
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CLOCC	Chemotherapy and Local Ablation Versus Chemotherapy
CT	Computed Tomography
ECOG	European Cooperative Oncology Group
ER	Emergency Room
HPB	Hepato-Pancreato-Biliary
HR	Hazzard Ratio
IQR	Interquartile Range
LHIN	Local Health Integration Network
MRI	Magnetic Resonance Imaging
MUST	Malnutrition Universal Screening Tool
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OR	Odds Ratio
pRBC	Packed Red Blood Cells

PROGRESS	Perioperative Optimization with Nutritional Supplements in Patients Undergoing Gastrointestinal Surgery for Cancer
QoL	Quality of Life
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
RA	Research Assistant
RESECT	Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases
SD	Standard Deviations
Th	Lymphocyte T Helper
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
FACT-G	Functional Assessment of Cancer Therapy – General
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FOLFIRI	Folinic acid-Fluorouracil-Irinotecan
b-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
PTT	Partial thromboplastin time
INR	International Normalized Ratio
CEA	Carcinoembryonic Antigen

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich thesis". It is built around four individual projects prepared for publication in peer-reviewed journals. Pablo Serrano contributed to all projects of this thesis in the following manner: conception of the research question, design of the study, work associated to funding the study, acquisition of data, analysis, and interpretation of data; and drafting the manuscript. The co-authors of each chapter contributed to the design of the study, execution and revising the manuscript critically for important intellectual content prior to submission to a peer-reviewed journal. The work of this thesis was performed between July 2016 and March 2022.

The original concept of this thesis work was different. It was based on a prospective cohort study evaluating the incidence of postoperative venous thromboembolism following gastrointestinal cancer surgery, a systematic review and meta-analysis of the same incidence, and the feasibility of a randomized controlled trial of extended (post-hospital discharge) venous thromboembolism prophylaxis versus placebo following gastrointestinal cancer surgery. However, the results of the cohort study and systematic review demonstrated that a randomized trial was not feasible given the low incidence of events. This work that was performed between September 2014 and July 2016 (i.e., cohort study and systematic review) was not included in this thesis.

CHAPTER 1.

1.1.Background

Surgical clinical studies are a type of clinical study design that involves patients undergoing a surgical intervention, where an intervention is defined as "*the physical change of body tissues through manual operation such as cutting, abrading,* or *suturing*"(Cook, 2009). These studies can be categorized into two main groups: experimental (i.e., randomized clinical trials) and observational. The United States' National Institutes of Health defines an experimental clinical trial as any "*research study in which one or more human participants are prospectively assigned to one or more* [surgical] *interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes*".(NIH, 2019 (cited 2020 Nov 27) Available from: https://grants.nih.gov/policy/clinical-trials/definition.htm) Surgical observational studies on the other hand, investigate outcomes of patients who will receive or have received a surgical intervention as part of their standard of care. Some examples of observational studies include: prospective cohort studies, retrospective cohort studies, case control studies and case series.(Del Fabro G, 2019 (avaliable from: https://doi.org/10.1007/978-3-030-05120-4. Springer) There are two different types of surgical clinical trials: 1) trials that investigate different medical therapies among surgical patients, in which although surgery is involved, it is not one of the interventions under investigation (which comprise 55% to 75% of all surgical clinical trials), and 2) trials that investigate different surgical procedures or surgical interventions, which could include

comparing surgery to observation.(McCulloch et al., 2002; Solomon & McLeod, 1998; Wente et al., 2003)

Surgical clinical trials are traditionally considered to be more difficult to perform compared to medical clinical trials (i.e., studies investigating medical drugs).(Rosenthal et al., 2015) One finding that suggests that clinical trials in surgery are more difficult to perform compared to medical trials is *the lower proportion of published surgical clinical trials that are randomized controlled trials*. In a study performed by Wente et al, only 3.4% of all publications in leading surgical journals were clinical trials, while over 80% were case reports and single institutional small series, a finding that has not significantly improved over time.(Gelijns et al., 2009; Horton, 1996) Some authors have suggested that as high as 25% of patients found in surgical wards receive treatments based on clinical trials, compared to up to 50% in medicine wards.(Ellis et al., 1995; Howes et al., 1997) Although this poor quality of published literature in surgery can be regarded as a measure of the difficulty of performing surgical trials, it is a multifactorial issue, that perhaps is more abstract and therefore more difficult to quantify and explain.(Serrano et al., 2021)

The most common objective finding that has been used to measure this higher degree of difficulty of surgical trials, is *the higher discontinuation rate of surgical compared to medical clinical trials*. In a study involving 863 protocols for randomized controlled trials submitted to 6 different research ethic boards (15% surgical and 85% medical), surgical trials were discontinued more often than medical trials, 43% versus 27%, risk difference 16%, 95% confidence interval (CI): 5 to 26, p=0.01.(Rosenthal et al., 2015) Another study showed that up to one in five surgical trials found in the clinicaltrials.gov database were

discontinued (or early terminated) and one in three completed surgical trials remain unpublished.(Chapman et al., 2014) Another study reviewed the website "clinicaltrials.gov" and reported a discontinuation rate of 11% in non-surgical trials compared to 16% in surgical ones.(Mouw et al., 2018) The most commonly cited reason for this higher discontinuation rate was: *slower recruitment in surgical trials compared to medical trials*. Recruitment has been defined as a multi-step and multi-disciplinary process or set of activities that are performed with the aim to complete enrollment to a clinical trial (i.e., accrual).(Kost et al., 2014) This same manuscript that reviewed protocols submitted to 6 research ethic boards, found that surgical trials were more often discontinued due to slow recruitment compared to medical trials, 18% versus 11%, risk difference 8%, 95% CI: 1 to 16, p=0.02.(Rosenthal et al., 2015) And in the review of "clinicaltrials.gov", discontinuation due to poor recruitment was more commonly found in surgical trials (45% versus 35%, p<0.001).(Mouw et al., 2018) However, slower recruitment in surgical trials has not been consistently found across studies. Cook et al, reviewed 114 publicly funded trials in the UK and found that there was no clear evidence that surgical trials differ from medical trials in terms of recruitment activity.(Cook et al., 2008)

For both, medical and surgical trials, slow recruitment is one of the most cited challenges leading to discontinuation. Time to accrue the first patient has been associated with the rate of recruitment throughout the trial; centres that take longer than one year to recruit the first patient tend to have a very slow rate of recruitment.(Haidich & Ioannidis, 2001) In a study from the UK, of 114 trials reviewed between 1994 and 2002, less than 1/3 achieved their original enrollment target, with 53% being awarded an extension. The

proportion of studies achieving their target sample size did not appear to improve over time. Recruitment start time was delayed in 47 (41%) trials and early recruitment problems were identified in 77 (63%) trials.(McDonald et al., 2006) In this study, some of the factors that were more commonly associated with higher accrual rate or that were found to increase accrual included: 1) interventions not available outside the trial, odds ratio (OR) 1.66, 95% CI: 0.58 to 4.76, 2) dedicated trial manager, OR 3.80, 95% CI: 0.79 to 36.14 and, and 3) being a cancer or drug trial, OR 2.7, 95% CI 1.11 to 6.93.(McDonald et al., 2006)

Some general interventions that have been suggested to increase recruitment include: incentives to motivate patients, training of recruiters, monthly newsletters, flyers to clinical staff and / or patients, phone calls to wards and sites, attending international congresses to update trial enrollment rates, as well as, public access to website with up-to-date information on enrollment.(McDonald et al., 2006; Treweek et al., 2013) The use of incentives to motivate patients to participate in studies can be classified as: 1) tangible incentives, such as paying for the cost of travel, parking or for the time involved in study participation, and 2) intangible incentives: encourage patient's self-motivation and feelings associated with greater benefit to society, continuity of participant-clinician relationship and perception of a greater level of care.(Featherstone & Donovan, 1998; Haidich & Ioannidis, 2001; Treweek et al., 2013)

This chapter will describe the methodological challenges of a surgical clinical trial that could lead to early discontinuation of the trial due to slow recruitment rates. These methodological challenges, although not unique to surgical clinical trials, are described within the context of a surgical trial (i.e., study population, study intervention, enrollment,

outcomes, etc.). The second portion of this chapter describes factors influencing recruitment that are unique to surgical clinical trials (i.e., timing of the study in relation to the development of the surgical procedure, patients', referring physicians' and surgeons' preferences regarding the intervention).

1.2.Methodological Challenges Influencing Recruitment

1.2.1. Study Population

Strict inclusion criteria are sometimes preferred in surgical clinical trials, to have a more homogeneous population and therefore decrease variability, thereby, increasing the power of the study, however, it may also slow accrual to a surgical trial.(Lilford et al., 2004; McCulloch et al., 2002) Surgical trials already limit the study population as surgical therapy is only indicated in some patients with the disease (i.e., comorbidities precluding surgery) and some patients thought to be eligible may become ineligible for the intervention once they are already in the operating room, a challenge that can affect both types of surgical trials.(Bonchek, 1997; Haynes RB, 2006. Lippincott Williams & Wilkins; Howes et al., 1997) Surgical oncology trials are more restrictive than other surgical trials as they only include patients with a diagnosis of cancer, therefore limiting the eligible population for the trial and adding the variable of time to the equation (i.e., patients with cancer require surgery in a timely manner).(Evrard et al., 2016) For example, in the RESECT trial, patients were enrolled in a trial involving simultaneous resection of colorectal cancer and liver metastases, however, of all participants enrolled, only 78% of them were eventually able to undergo simultaneous resection due to intraoperative findings (progression of disease, bleeding leading to shock, intraoperative death, etc.). Therefore, when considering the

sample size in a surgical trial, one must also take into consideration and identify the proportion of participants that although enrolled, will not be able to undergo surgery (i.e., the study intervention), which must be known a priori. This proportion varies depending on the type of procedure performed and the indications (i.e., 30% of patients with pancreatic cancer are not able to undergo pancreaticoduodenectomy due to intraoperative findings related to tumour progression).(Bilimoria et al., 2007; Conlon & Brennan, 2000) Therefore, to the traditional ideal study population for any clinical trial (i.e., patients with high event rates of the target condition, high compliance to the intervention and high responsiveness of the treatment in question), for a surgical trial, one must also add the resection rate.(Kan & Kestle, 2007) It is important to determine the correct sample size before starting the trial so that if needed, other sites are added to finish accrual in a timely manner.

1.2.2. Study Intervention

There are two different types of surgical trials: 1) trials that investigate different surgical procedures or surgical interventions, and 2) trials that investigate different medical therapies among patients undergoing surgery, in which although surgery is involved, it is not the intervention under investigation. This latter type of trial is the most commonly found in the surgical literature and comprise 55% to 75% of all published surgical trials. They are also thought to be less challenging to perform.(McCulloch et al., 2002; Solomon & McLeod, 1998; Wente et al., 2003)

Surgical trials that investigate surgical interventions can be classified into three different sub-categories based on the magnitude of the difference between comparators, as issues with compliance and clinical equipoise are higher when the difference between

interventions is greatest.(Bonchek, 1997; Cook et al., 2008; Wartolowska et al., 2016) The three sub-categories based on a perceived increasing level of difficulty to conduct are: 1) Level 1: studies comparing surgical procedures that differ only slightly (i.e., comparison of two methods of pancreas anastomosis or applying a patch to the distal pancreatic stump),(Hassenpflug et al., 2016; Keck et al., 2016) 2) Level 2: studies comparing different ways to perform an operation, involving significant differences such as the overall approach and skills (i.e., open versus laparoscopic liver resection or simultaneous versus staged colon and liver resection for colorectal cancer metastases),(Fretland et al., 2018; Serrano et al., 2018) and 3) Level 3: comparison of medical (or observation) versus surgical treatment (i.e., trial of carotid endarterectomy versus best medical management or a trial of surgical fundoplication versus proton pump inhibitors for gastrointestinal reflux disease).(Mahon et al., 2005; North American Symptomatic Carotid Endarterectomy Trial et al., 1991) Level 1 and Level 2 studies usually deal with some type of surgical innovation, where innovation is defined as a "new or modified surgical procedure that differs from currently accepted local practice, the outcomes of which have not been described, and which may entail risk to the patient".(Barkun et al., 2009) It is recommended that all types of surgical innovation be scientifically studied prior to implementation, although the term scientific is loose and not always follows a clear path, there are some recommendations on the types of studies that should be performed to evaluate surgical innovation based on the "timing" of the development of the innovation (see section 1.3.1).(Ergina et al., 2009; McCulloch et al., 2009)

1.2.3. Blinding Methods

Although blinding is generally recommended as a method to decrease bias in randomized trials, most surgical trials that compare surgical interventions lack blinding.(Kan & Kestle, 2007) On the other hand, surgical trials that compare a medical intervention or when the intervention includes only a small portion of the surgery, are somewhat easier to blind.(Whitlock et al., 2021) This lack of blinding in surgical trials, affects their internal validity as it can be associated with different types of bias: performance bias (concurrent interventions depending on allocation), attrition bias (differential withdrawal from follow-up), ascertainment bias (differential assessment introduced by evaluators or investigators) and, detection bias (differential outcome assessment).(Ergina et al., 2009; Lilford et al., 2004)

A Cochrane Review on medical and surgical trials, found that open label trials were more effective in increasing recruitment compared to placebo-controlled trials, risk ratio (RR): 1.2, 95% CI 1.09 to 1.36.(Treweek et al., 2013) Interestingly, a systematic review of 63 different surgical trials that had a placebo arm reported that many of the challenges described by these trials were not associated with the fact that they had a placebo arm (funding, anesthesia, blinding of patients and assessors), but rather, challenges relevant to other surgical trials in general (i.e., difficulty in finding eligible patients).(Wartolowska et al., 2016) However, it is generally thought that recruitment to placebo controlled trials is more difficult to perform compared to open arm controls.

Some authors argue that patients are often less keen to participate in a study in which there is a possibility of a placebo intervention, an issue that is mostly related to

medical trials that involve surgical patients since randomized surgical trials that compare surgical interventions are notoriously difficult to blind, moreover, to blind to a placebo intervention.(Halpern et al., 2002; Hare et al., 2014; Howes et al., 1997) Despite the common thought that blinding patients, surgeons and outcome assessors is often difficult in surgical trials and that the ethics of performing a sham operation is open to debate, several surgical trials have been performed using a placebo-controlled design (sham-controlled surgical trials).(Dowrick & Bhandari, 2012; Wartolowska et al., 2016) Some of these trials have been crucial, as they avoided ineffective treatments from becoming standard practice, as is the case with the use of internal mammary artery ligation for the treatment of angina pectoris.(Cobb et al., 1959) While some other trials have not changed surgical management despite showing no superiority over a sham surgical procedure (i.e., arthroscopic lavage or debridement for the treatment of osteoarthritis).(Hawker et al., 2008; Moseley et al., 2002)

If a sham-controlled trial is being developed, it is recommended that researchers discuss in detail four different principles in their protocol: 1) equipoise, 2) how to minimize risk for the patient, 3) clear description of informed consent and 4) how the surgeon will deal with patient blinding over the follow-up period (principle of "deception").(Dowrick & Bhandari, 2012) Sham-controlled surgical trials are still being performed, as the discussion of ethical issues continues to evolve. Currently, the decision to proceed with a sham-controlled surgical trial relies on the local research ethics board.

1.2.4. Statistical Considerations

1.2.4.1. Sample Size and Feasibility

The planning of a surgical trial should include a thorough assessment of the institution's realistic expectations of accrual, based on incidence of cases, potential eligible participants (based on inclusion / exclusion criteria), potential eligible participants who would agree to enroll and as previously mentioned, the proportion of patients expected to complete the intended surgical intervention, which varies according to the type of surgical procedure and patient population. The calculation of sample size should include an over-estimation of the number of patients available for the study and who will agree to participate, considering that study participation is usually 10% of all screened patients.(Howes et al., 1997) And of those that are eligible for the study (based on inclusion / exclusion criteria), only 50% end up participating, usually due to patient and surgeons' preferences, timing of the intervention, among other issues described in this thesis.(Howes et al., 1997) It is very common for clinicians to overestimate the number of patients potentially eligible for study participation, a finding that has been named "Lasagna Law" or "Muench's Third Law".(Lasagna, 1979) Some authors have also suggested to take into consideration the "number of patients needed to screen", which sometimes can be as high as 5.5 times the number of participants eventually included in the study (for a study comparing surgical versus no surgical treatment).(Frobell et al., 2007) This overestimation can lead to slow recruitment in a multicentre trial, if researchers avoid adding alternate centres.(McDonald et al., 2006)

When calculating the sample size of a study, some authors recommend to first estimate the number of patients that can be enrolled in the study, also called: "patients I can get". From this number, then specify a range of reasonable differences in event rates between control and intervention group (also called delta) and pick the acceptable degree of type I error (typically alpha=0.05). This method will create different levels of power (1-beta) according to each delta. Sometimes, the power of the study may need to be lowered in order to achieve a realistic sample size.(Haynes RB, 2006. Lippincott Williams & Wilkins)

Specifically related to surgical trials that compare a surgical intervention, high variability is often an issue, especially at the beginning of the learning curve of the surgical intervention. This increase in variability will inevitable decrease the power of the study and therefore increase the required sample size to reject the null hypothesis and detect a difference between groups.(Haynes RB, 2006. Lippincott Williams & Wilkins)

It is commonly reported that study completion is more likely in multicentre studies.(Howes et al., 1997) Multicentre trials, although important to improve generalizability, introduce a certain degree of variability, as the level of skills of the surgeon and anesthesiologists as well as the surgical team vary between centres.(Stirrat et al., 1992) This variability can be controlled to a certain degree by randomization stratified by site. Contrary to an intuitive approach to site selection, having opinion leaders, experience with previous surgical studies, and publication record may not predict the recruitment ability of a site.(Flodgren et al., 2019; Foy et al., 2003) Moreover, clinical trials of surgical innovation led by opinion leaders can have some difficulties in accrual if the opinion leader

is not trained in research methodology and is not keen on clinical trials.(Denost et al., 2014) Some authors suggest that the key factor to select a site is the presence of a motivated surgeon that can act as the principal investigator, which sometimes has been characterised as a junior faculty member with sufficient protected research time. It is also important to have a good project manager for clinical trials.(Mills et al., 2003; Thoma et al., 2010) Most scholars agree that studies that involve a network of interdisciplinary teams, such as trial methodologists, statisticians, data managers and trial managers have lower rates of discontinuation.(Rosenthal et al., 2015) It is also important to consider whether sites work within a publicly or privately funded health care system as this may influence participation and enrollment, as some insurance carriers may refuse to pay for an intervention that has not been proven to be effective.(Mills et al., 2003; Thoma et al., 2010)

Pilot studies have been recommended as effective means to evaluate particular study aspects such as recruitment, resource utilization and protocol feasibility. Pilot studies can also be used to identify protocol (i.e., inclusion criteria), site- and investigator-specific issues, to determine adherence of the investigators and patients to the study protocol, to obtain an estimate of patient follow-up and drop-outs as well as to collect preliminary data to calculate sample size.(Mills et al., 2003; Rosenthal et al., 2015; Thoma et al., 2010) Also, the enrollment fraction of pilot studies can predict the number of sites that will need to be opened in the larger trial. Data from pilot studies could be used in the larger trial if the data is unblinded and if it is a pre-specified objective. Most importantly, in order to use pilot data into the main trial, the changes incorporated into the pilot trial must be congruent with the final study.

1.2.5. Ethical and regulatory standards

1.2.5.1. Informed consent

Obtaining consent is usually one of the first steps in the accrual process (following screening). This first introduction of the trial is therefore crucial for trial recruitment and could be the limiting factor affecting accrual to a study.(Stirrat et al., 1992) Although it is important to engage the patient in the consent process, it is also paramount to fully explain the potential risks of participating in the trial to the patient and how it would differ from standard of care (i.e., surgical procedure alone without being on the trial). Some authors suggest having a standard script when consenting patients over the phone or in person, that includes answers to potential questions or concerns about the study. However, strategies comparing different ways to deliver the consent process have failed to identify a preferred approach that improves recruitment (i.e., reading out loud, timing of consent, video consent, providing supplementary material, etc.).(Treweek et al., 2013)

Persistent attempts to include patients in a study may hurt patient-doctor relationship as patients may think their physician is mostly attentive to the study rather than the patient's own best interest.(Featherstone & Donovan, 1998; Haidich & Ioannidis, 2001) Lack of standardized consent methods can lead to discrepancy and / or incomplete disclosure of risk and benefits, especially if surgeons have strong preferences for one treatment over another.(Sibai et al., 2012) Although the consent process is typically performed by trained research personnel that do not take part in treatment decisions for the patient, it is the role of the treating surgeon to introduce the study to the patient. Patients

may be willing to participate in the study based on the enthusiasm of their treating surgeon for the study. Previous studies have shown that removing the treating physician from the consent process increases the proportion of patients who are willing to participate in a surgical trial.(Donovan et al., 2002) The language used in the consent process should be simple and easy to understand, i.e., it is better to talk about "toss of a coin" instead of "random allocation".(Etchells, 1999)

It is important to understand that for surgical clinical trials that involve a sham procedure, obtaining informed consent does not justify its ethics. This is true, even after considering that all risks would be minimized if patient is randomized to a sham surgical procedure (i.e., minimizing exposure to radiation, bleeding, infection, general anesthesia, etc.).(Dowrick & Bhandari, 2012)

1.3.Factors Unique to Surgical Clinical Trials that Influence Recruitment

1.3.1. Timing of the Trial

The timing of the trial in relation to the development of the surgical procedure or surgical intervention is crucial, affecting all types of surgical trials, but mostly surgical trials that investigate surgical procedures.

Many procedures become standard of care without prior clinical trial evaluation. This proliferation of surgical innovation on the basis of limited and weak scientific evidence has been linked to the absence of regulatory bodies for surgical procedures and interventions.(McCulloch et al., 2009) Unlike drugs that need to be thoroughly tested prior to adoption, surgeons can proceed with new techniques and operations with little constraint, even from their own institution's ethical committee or administration.(Solomon &

McLeod, 1993; Stirrat et al., 1992) There are different stages of evaluation of a surgical innovation, starting from the innovation stage, that describes "*the first use of a new procedure in a patient prompted by the need for a new solution to a clinical problem*". This is followed by the "development phase", in which the surgery is performed in a small number of patients, then by the "exploration phase", that happens once the procedure has been described and the main technical aspects worked out. The assessment stage compares the new procedure to the current surgical standard, ideally, a randomized clinical trial.(McCulloch et al., 2009)

The uptake of surgical innovation without scientific evidence tends to be different across geographical areas.(Diehr et al., 1993) Different theories have been proposed to explain this phenomenon, including Chassin's hypothesis of "small area rate variations", which suggests that high-uptake areas are associated with the presence of surgeons with high enthusiasm for the procedure of interest (i.e., opinion leaders).(Chassin, 1993) A recent population-based study in Ontario suggested that the greater use of laparoscopic liver resection in certain geographical areas was due to a relative enthusiasm for that procedure among a small number of opinion leader surgeons.(Wang et al., 2020) The adoption of surgical procedures prior to rigorous research evaluation can lead to the widespread uptake of a procedure that may cause harm, such as the adoption of laparoscopic pancreaticoduodenectomy.(van Hilst et al., 2019)

If the trial is performed late in the uptake process of the procedure, the indications for the procedure may be clearer and the risks may be lower, and, it is also possible that the procedure may no longer be relevant or that the procedure may have already be established

by the community of surgeons, in which case, the study becomes "unnecessary" as surgeons and patients may already have a preference, (i.e., lack of equipoise).(Bonchek, 1997; McCulloch et al., 2002; McLeod, 1999; McLeod et al., 1996) This was nicely described as the Buxton's law ("it is too soon for a trial, until it is too late").(Barkun et al., 2009) Some examples of delayed timing of surgical trials in relationship to the uptake by the surgical community include: 1) the NASCET trial, which was performed even when the procedure (i.e., carotid endarterectomy) had already gained popular acceptance (North American Symptomatic Carotid Endarterectomy Trial et al., 1991) and 2) laparoscopic cholecystectomy, which was widely accepted by the surgical community without being evaluated in large clinical trials.(Majeed et al., 1996) Likewise, delayed initiation of a study could lead to a lack of referral of patients to institutions that are trialing the procedure, as referring doctors may know that the procedure in question can be performed at a different institution without the need of a trial (see section 1.3.5; referring physician preference), as was seen in the CLOCC trial, that compared the use of radiofrequency ablation (usually performed intraoperatively) and systemic chemotherapy to systemic chemotherapy alone for colorectal cancer liver metastases; the trial became obsolete when radiofrequency ablation was available outside of the trial and chemotherapy regimens changed by including biological treatments.(Bonchek, 1997; Evrard et al., 2016) On the other hand, if the intervention in question can only be performed within the trial, then participation and recruitment will probably be better as patients and referring physicians would want patients to try the new technology, as was the case with the REMATCH trial, that evaluated the use of a left ventricular assist device.((US Institute of Medicine), 2012; Rose et al., 2001)

1.3.2. Standardization of the Surgical Intervention

Unique to surgical trials compared to medical trials, is their dependence on the technical skills of the surgeon as the clinical investigator.(Haynes RB, 2006. Lippincott Williams & Wilkins; Lilford et al., 2004) New technical modifications, individual preferences and improvements of perioperative care are prone to happen as the procedure evolves, influencing the outcome of patients undergoing such procedures.(Lilford et al., 2004) Postoperative outcomes, such as postoperative complications, readmission, and postoperative mortality are, by definition, dependent on the skill of the surgeon and / or of the surgical team as a whole with a specific procedure.(Cook et al., 2013) Outcomes tend to improve with extensive experience, therefore with time.(Birkmeyer et al., 2002; Devereaux et al., 2005; Ergina et al., 2009) This improvement of performance over time is called "learning curve", and this learning curve affects surgeons of all skill levels, from poorly skilled to highly skilled surgeons. The learning curve has two different components: 1) the community or technology learning curve: as technology evolves and technique develops, the refinement of the new intervention increases and 2) the personal learning curve of the individual surgeon, which is often driven by personal attitudes, their surgical training, and their professional experience. Medical trials, and even medical trials in surgical patients, have the advantage of a more standardized process. Medication dosages are standardized, and the measurement of compliance and side effects is predictable.(McLeod et al., 1996) Instead, variability in the skill level of individual surgeons leads to less standardization in surgical trials and higher statistical variance. This higher variability can decrease statistical power and could also lead to challenges to

complete the study as poor surgical outcomes could stop accrual to a study.(Fielding et al., 1978; van Hilst et al., 2019; Wente et al., 2003)

This variability in surgeon's expertise is an important trait of pragmatic or effectiveness trials, which aim to replicate common surgical practice. On the other hand, explanatory or efficacy trials are usually performed by a small group of surgeons that are often experts in the field, and although they are best suited to test an intervention, their results may not be generalizable to the population of interest.(Lilford et al., 2004; Thoma et al., 2010) These explanatory trials are best suited for the initial evaluation of an intervention or the beginning stages of the development of a specific surgical procedure, when the study investigator wants to determine feasibility and applicability.(Devereaux et al., 2005) Pragmatic designs on the other hand fit more with reality, are more widely applicable and answer the question: "is this surgical procedure effective when performed by many different surgeons without special expertise?".(McCulloch et al., 2002; McLeod, 1999)

Most authors suggest that standardization of the surgical intervention is important in any surgical trial. In order to have more standardization in a clinical study, it is recommended that surgeons perform a minimum number of the specific surgical procedure prior to the initiation of a clinical trial, that surgeons have a minimum professional and training level (i.e., hepatobiliary surgical training), and / or that the learning curve is measured using CUSUM tests (for assessment of complications over time).(McCulloch et al., 2002; Wente et al., 2003) Standardization of a specific surgical procedure (which, in a randomized trial, should include standardization of the surgical intervention as well as

standardization of the control procedure) can also be achieved by study-specific in-person training of the critical aspects of the procedure, intra-procedure videos, pictures or manuals describing how the procedure should be performed. It is generally not recommended to include patients into a trial in which the surgeon is not properly trained in the specific intervention.(Chalmers, 1975) It is key to standardize the perioperative care as well (preoperative antibiotics, venous thromboembolism prophylaxis, preoperative chemotherapy, etc.), all with the intent to leave the effect of the surgeon as a variable as minimal as possible.(Howes et al., 1997; McLeod, 1999)

Expertise-based clinical trials have been postulated as an alternate solution to the different learning curve of surgeons and as a type of explanatory clinical trial.(Devereaux et al., 2005; Thoma et al., 2010) In these trials, patients are allocated to expert surgeons performing the intervention to which they were randomized. This method prevents differential expertise bias, a bias that is introduced by the preference of each surgeon to a specific procedure (thereby attempting to limit the influence of the surgeon on the outcome). Even if the surgical community as a whole can be in equipoise for a specific surgical procedure, individual surgeons may have a strong preference of one procedure over another, and therefore, they may tend to be more meticulous or attempt more co-interventions on patients randomized to their surgical procedure of preference.(McCulloch et al., 2002) Expertise-based trials may also avoid differential procedural cross-over (i.e., different rate of cross-over between arms).(Bonchek, 1997; Sibai et al., 2012) These types of trials are thought to be especially relevant to evaluate different types of surgical techniques (i.e., minimally invasive versus open technique) given that there is evidence of

small area rate variations with these types of procedures.(Wang et al., 2020) Expertise-based trials have been applied successfully in orthopedic procedures comparing different techniques of insertion of a fixation device.(Alobaid et al., 2004) Although initially postulated in 1980, a recent meta-analysis revealed that expertise-based trials have not gained popularity across different specialties, including surgery.(Cook et al., 2015; van der Linden, 1980) The use of propensity score matching in cohort studies can be an alternative to randomized trials where expertise bias is an important confounding factor.

1.3.3. Patient Preferences

Patients are key stakeholders in the planning phase of a study, as they may have pre-conceived opinions of the study intervention in question, which may lead to refusal to participate in a surgical study (lack of equipoise from patient's perspective).(Howes et al., 1997; Kennedy et al., 1998; Stirrat et al., 1992) Refusal to participate is usually a bigger problem in surgical trials that evaluate surgical interventions, and within that group, refusal is even higher for trials that compare a surgical intervention to a medical therapy (or even observation) as patients may fear the surgical intervention "is too aggressive" or that the risk of surgery is considered to be much higher.(Solomon & McLeod, 1998) Surgical trials are also unique in the sense that patients may perceive they have limited options for cross-over (as compared to medical studies) given the irreversibility of surgery.(Featherstone & Donovan, 1998; Haidich & Ioannidis, 2001; McLeod et al., 1996) One approach that has been suggested to increase patient recruitment is the Zelen design, which was used in a surgical trial comparing lumpectomy to mastectomy for breast cancer.(Blichert-Toft et al., 2008) In this type of randomized trial, patients are allocated into two groups (prior to patient

consent) by random allocation. Patients in the first group receive standard treatment, while patients in the second group are invited to participate in a trial receiving the experimental intervention. If patients decline the experimental therapy, then they would be treated with the standard treatment. At the end, patients in the first group are compared to the second group regardless of treatment allocation.(Zelen, 1979) This approach has not been widely utilized in surgical trials, mostly due to its ethical controversies.(Homer, 2002)

Some feasibility studies have found that patients may not wish to leave the decision of their treatment to chance or uncertainty, in the case of randomized trials.(Mills et al., 2003) It is also possible that patients prefer the surgical treatment to medical therapy if surgery is considered to be the "best" option for cure, alternatively, patients may prefer the less invasive treatment (i.e., chemoradiation therapy), if the alternative is a high risk surgery.(Kennedy et al., 1998; McCulloch et al., 2002) For example, observational studies of patients with oropharyngeal squamous cell carcinoma have found that the overall survival is similar between patients who undergo upfront surgery versus definitive chemoradiation therapy.(Kelly et al., 2017) A recent clinical trial comparing both arms was withdrawn after it failed to accrue enough patients eligible for the study. (FC) 2021, available from: https://clinicaltrials.gov/ct2/show/NCT01953952) Therefore, surgical trials seem to polarise participant attitudes for and against surgery for different reasons.(Cook et al., 2008; Stirrat et al., 1992)

Patients may also prefer one type of surgical procedure versus another, and this preference may come from their own research on the internet or social media, from the opinion of their trusted physicians (i.e., family doctor) or from the interactions they have

with their treating surgeon (i.e., patients may sense that their surgeon has a preference of one procedure over the other).(Evrard et al., 2016; "Surgical research: the reality and the IDEAL," 2009) A study of open versus laparoscopic versus robotic cystectomy was deemed not feasible after a pilot study failed to reach the accrual target as patients had a preference of one procedure over the other and they were able to get that procedure outside of the clinical trial.(Harrop et al., 2016) This shows the difficulties of trying to enroll patients in surgical clinical trials of innovative interventions when the innovative intervention is available as standard of care elsewhere (Section 1.3.1). Some patients may not be willing to travel long distances to a tertiary care cancer centre for the main purpose of being enrolled in a clinical trial, when they can receive treatment closer to home.(Lamont et al., 2003) Recently, with the development of telemedicine with the COVID-19 pandemic, some clinical trial sponsors are allowing patients to receive the intervention in alternate centres outside of the cancer centre as long as the alternate centre agrees to participate in the clinical trial procedures and patients agree to be followed using telemedicine.

It is inconclusive if other patient factors, such as patient level of education, age, wealth, and patients' confidence with their physician are potential barriers to patient participation in a surgical trial.(Prescott et al., 1999; Ross et al., 1999) Patients' perception of the risk from their disease could be a limiting factor for participation in surgical trials; patients with worse outlook towards disease might be less likely to consent to a study. Some authors have suggested that cultural factors, such as the country of origin (European Union versus North America) is associated with a higher participation rate in clinical trials, although this concept has not been studied in detail, it is clear that most surgical trials

originate from European countries even though, most of the journals where they are published are based in North America.(Robinson et al., 2021) Some studies have suggested differences in study regulations (by ethics committee), study costs, and other aspects of study conduct between regions as the likely cause of the suspected variation in patient participation between these two regions.(Mackintosh DR, 2001; NJ, 2004) Participants' trust with the healthcare system can also drive recruitment as some populations may feel disengaged with the health care system. Some have suggested the use of education materials that are culturally and linguistically relevant for the population of interest, however this has not been tested widely.((US Institute of Medicine), 2012)

1.3.4. Surgeon Preferences

There is a large body of literature that attempts to investigate if surgeons are less motivated to include patients in trials when compared to other clinicians. Some barriers to recruitment are general to all clinicians and not unique to surgeons, i.e., time constraints, need for ethics approval, development of a more complex consent process, discussion of uncertainty with patients, more intense follow-up, lack of staff and lack of training of clinicians in trial methodology and statistical methods, loss of professional autonomy, lack of rewards and recognition, among others.(McLeod et al., 1996; Ross et al., 1999) There are others factors that are only applicable to certain health care systems (i.e., fee for service); some surgeons could see an economic disadvantage if patients were randomized to a non-surgical arm. Surgeons may also fear a loss of their referral base; if they do not adopt a specific surgical procedure that has been taken up by the community of surgeons (i.e., surgeon's reputation in the community is placed into question).(Evrard et al., 2016)

For a randomized clinical trial to be successful, surgeons must have equipoise. Usually, there is equipoise when there is a lack of scientific data for a particular surgical procedure. This equipoise (particularly for surgical procedures and less so for medical interventions involving surgical patients), is sometimes difficult to find among surgeons, with some authors suggesting that one of the reasons for this lack of equipoise is that surgeons tend to rely on the results of case series and intuition to guide their treatment options, since most surgical procedures have been adopted without the back up of a clinical trial.(Howes et al., 1997)

Some authors have suggested that surgeons, when compared to medical physicians are less tolerant to uncertainty (a key principle of any clinical trial) and therefore avoid having discussions with patients about the uncertainty of a surgical procedure.(McCulloch et al., 2005; Sibai et al., 2012) This intolerance to uncertainty may stem from the traditional master-student model of surgical training, in which the "master" (or surgeon) is supposed to "know everything", therefore, new techniques are often not utilized following evidence.(Ergina et al., 2009) A large survey among surgeons involving patients in a surgical trial for breast cancer (comparing segmental mastectomy and postoperative radiation therapy to segmental mastectomy alone and total mastectomy) identified self-reported key reasons for low accrual to this trial.(Taylor et al., 1984) Among all the reasons, the most common one, was related to concerns that the doctor-patient relationship would be affected (73% of respondents). This survey noted that clinical studies, specifically randomized trials, have the potential to compromise the perceived authority of the surgeon

by limiting their expert knowledge and individualized decision-making power. However, this study is over 40 years old and surgeons' perceptions may have evolved since then.

Multiple studies have suggested that the opinion of the treating surgeon towards a clinical trial is the most important factor that affects accrual (i.e., strongly-held beliefs in favour or against the trial), as patients tend to trust the opinion of their treating physician.(Kaas et al., 2005) The surgeon's opinion of a clinical trial and therefore the eligibility of their patients to a clinical trial can be modified prior to making a treatment decision by the way of a multidisciplinary discussion at tumour boards, therefore presenting cases at tumour boards can increase patient accrual to clinical trials.(Kuroki et al., 2010) It is also important for surgeons to communicate with patients the existence of clinical trials for which their patients may be eligible for.(Arnaout et al., 2016) Some suggest that patient education sessions (in the forms of pamphlets mailed to patients) prior to their appointment with their treating surgeons may improve accrual to trials by eliminating the role of the surgeon in communicating possible clinical trials to their patients.(Wallace et al., 2006) However, most authors agree that surgeon's opinion on a possible clinical trial for their patients is one of the most important aspects that influence patient's decision to participate in a trial.(Siminoff et al., 2000)

1.3.5. Referring Physician preferences

The referring physician is a key member of a surgical clinical trial as it is rare for surgeons to be the first point of contact for a potential participant, unless the trial is set in a hospital setting (i.e., emergency room). Patients usually trust the opinion of their first point of contact with the health care system, especially if it is their family physician, a physician

with whom they already have a previous relationship. However, a referring physician can also be from a different specialty, including gastroenterologists, cardiologists, or even surgeons that are not part of the clinical trial organization (i.e., community surgeons).

As discussed above, referring physicians may not wish to refer patients to an institution where a clinical trial is being offered if they know that same intervention can be offered somewhere else outside the trial (i.e., timing of the intervention). Therefore, education and communication of trial procedures, including trial enrollment and ways in which physicians can participate in the trial (including feedback), is necessary not only with physician trialists but also those surrounding the patients' circle of care, including referring physicians.((US Institute of Medicine), 2012; Arnaout et al., 2016; D'Alimonte et al., 2015) In this thesis, we explore a relatively new way to identify potential patients to a surgical clinical trial, by using population-based databases. Using these databases may eliminate the dependence on referring physicians to identify potential participants, however, it does not eliminate their role entirely, as they will always be the point of contact for patients, therefore, communication and education is vital. It is possible that some referring physicians prefer their patients to be in a trial as some studies have suggested that patients in a trial have better outcomes compared to clinical practice, which could be due to different reasons, among them, better quality of care offered when patients participate in trials.

1.3.6. Funding

Funding for surgical trials has always been considered an important issue that limits the possibility to perform high quality research in surgery. Some scholars have anecdotally cited that surgical trials have less funding opportunities compared to medical trials because

there is a relative lack of incentive from pharmaceutical companies due to lack of commercial interest. The proportion of public funding for surgical trials is significantly less (<5%) to that dedicated to "medical trials".(Evrard et al., 2016) It is also rare to have large multicentre surgical trials supported by publicly funded national bodies.(Johnson & Dixon, 1997; Kennedy et al., 1998; McLeod et al., 1996; Mills et al., 2003; Wente et al., 2003) Some surgical trials that test new devices (i.e., the left ventricular assist device in the REMATCH trial) may have dual funding (privately and publicly funded organizations), which can help finish the trial if recruitment is slow and funding runs out.((US Institute of Medicine), 2012; Rose et al., 2001) This lack of funding might also be responsible for the delayed initiation of a trial in relationship to the development of the procedure of interest (i.e., timing), as pointed out earlier.(McCulloch et al., 2002; Solomon & McLeod, 1993)

1.4.Summary of Chapters and Rationale

This thesis consists of four different manuscripts, including two different surgical clinical trials (one surgical trial comparing medical interventions and the other one, a surgical trial evaluating a complex surgical intervention), one population-based study describing a possible solution for recruitment to surgical trials, that was run alongside a surgical trial, and lastly the protocol of a surgical trial that compares two different surgical interventions, that incorporates the results of the previous studies. These studies are separated into four different chapters, beginning with Chapter 2. The second and third chapter present the manuscript, as it was published, and ends with a discussion section (and a table) added at the end of the manuscript, describing the specific recruitment challenge posed by the trial and the opportunity for improvement, based on the framework described

above. The fourth chapter include only the final manuscript as it was published, and the fifth chapter (protocol for a trial) is written in accordance with the requirements for publication by the International Journal of Surgery Protocols.

Chapter 2 describes the PROGRESS randomized trial. This is a single institution, double blind, placebo controlled randomized pilot feasibility clinical trial. It compares the use of perioperative nutritional supplements versus placebo for patients undergoing cancer surgery. Perioperative nutritional supplements are thought to improve nutrition by increasing protein intake to influence cell-mediated immunity, thereby potentially reducing the rate of postoperative infectious complications. This feasibility trial hypothesized that a large trial of perioperative nutritional supplements was feasible, and that this intervention would improve clinical and surgical outcomes (postoperative complications and quality of life). The aim was to estimate the feasibility of a large-scale trial (defined as feasible if enrollment rate was >60% throughout the trial). This chapter expands on issues related to recruitment to surgical trials comparing medical interventions among patients undergoing a surgical procedure.

Chapter 3 reports the results of the RESECT trial, a multicentre, single arm pilot trial, exploring the feasibility of enrolling patients to a surgical trial involving a surgical intervention: simultaneous resection of colorectal cancer and liver metastases. This chapter investigates challenges with accrual to a trial of a surgical intervention that could carry a high risk of complications and a potential loss of physician-patient relationship. It expands on challenges that are unique to surgical trials of a surgical intervention.

Chapter 4 proposes the use of population-based electronic databases (i.e., ePATH and OneView) as a possible solution to patient accrual to the RESECT trial, by eliminating the need for a surgeon to identify potential study participants and refer them to the clinical trials group (the ACCESS study). This study was performed in parallel to the RESECT trial and therefore served as a comparison to the number of patients enrolled by traditional methods to the number of eligible patients identified through databases.

Chapter 5 presents the protocol for a randomized controlled trial comparing simultaneous versus staged resection for synchronous colorectal cancer liver metastases (RESECT-RCT). It builds on the results of the RESECT trial to identify the patient population, outcome of interest and sample size. This protocol also incorporates the findings of the ACCESS study to improve trial accrual.

Chapter 6 discusses the lessons learned from the two different trials as a form of conclusion, examining possible solutions to the recruitment challenges described in this PhD thesis. This chapter also discusses limitations as well as future research planned based on this thesis work.

REFERENCES

(US), Institute of Medicine (2012). Public Engagement and Clinical Trials: New Models and Disruptive Technologies: Workshop Summary. *Washington (DC): National Academies Press (US)*, https://www.ncbi.nlm.nih.gov/books/NBK92105/.

Alobaid, A., Harvey, E. J., Elder, G. M., Lander, P., Guy, P., & Reindl, R. (2004). Minimally invasive dynamic hip screw: prospective randomized trial of two techniques of insertion of a standard dynamic fixation device. *J Orthop Trauma*, *18*(4), 207-212. https://doi.org/10.1097/00005131-200404000-00003

Arnaout, A., Kuchuk, I., Bouganim, N., Pond, G., Verma, S., Segal, R., Dent, S., Gertler, S., Song, X., Kanji, F., & Clemons, M. (2016). Can the referring surgeon enhance accrual of breast cancer patients to medical and radiation oncology trials? The ENHANCE study. *Curr Oncol*, *23*(3), e276-279. https://doi.org/10.3747/co.23.2394

Barkun, J. S., Aronson, J. K., Feldman, L. S., Maddern, G. J., Strasberg, S. M., Balliol, C., Altman, D. G., Barkun, J. S., Blazeby, J. M., Boutron, I. C., Campbell, W. B., Clavien, P. A., Cook, J. A., Ergina, P. L., Flum, D. R., Glasziou, P., Marshall, J. C., McCulloch, P., Nicholl, J., . . . Vandenbroucke, J. (2009). Evaluation and stages of surgical innovations. *Lancet*, *374*(9695), 1089-1096. https://doi.org/10.1016/S0140-6736(09)61083-7

Bilimoria, K. Y., Bentrem, D. J., Ko, C. Y., Stewart, A. K., Winchester, D. P., & Talamonti, M. S. (2007). National failure to operate on early stage pancreatic cancer. *Ann Surg*, *246*(2), 173-180. https://doi.org/10.1097/SLA.0b013e3180691579

Birkmeyer, J. D., Siewers, A. E., Finlayson, E. V., Stukel, T. A., Lucas, F. L., Batista, I., Welch, H. G., & Wennberg, D. E. (2002). Hospital volume and surgical mortality in the United States. *New England Journal of Medicine*, *346*(15), 1128-1137. https://doi.org/10.1056/NEJMsa012337

Blichert-Toft, M., Nielsen, M., During, M., Moller, S., Rank, F., Overgaard, M., & Mouridsen, H. T. (2008). Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol*, *47*(4), 672-681. https://doi.org/10.1080/02841860801971439

Bonchek, L. I. (1997). Randomised trials of new procedures: problems and pitfalls. *Heart*, *78*(6), 535-536. https://doi.org/10.1136/hrt.78.6.535

Chalmers, T. C. (1975). Randomization of the first patient. *Med Clin North Am*, *59*(4), 1035-1038. https://doi.org/10.1016/s0025-7125(16)32001-6

Chapman, S. J., Shelton, B., Mahmood, H., Fitzgerald, J. E., Harrison, E. M., & Bhangu, A. (2014). Discontinuation and non-publication of surgical randomised controlled trials: observational study. *BMJ*, *349*, g6870. https://doi.org/10.1136/bmj.g6870

Chassin, M. R. (1993). Explaining geographic variations. The enthusiasm hypothesis. *Med Care*, *31*(5 Suppl), YS37-44. https://doi.org/10.1097/00005650-199305001-00006

Cobb, L. A., Thomas, G. I., Dillard, D. H., Merendino, K. A., & Bruce, R. A. (1959). An evaluation of internal-mammary-artery ligation by a double-blind technic. *New England Journal of Medicine*, *260*(22), 1115-1118. https://doi.org/10.1056/NEJM195905282602204

Conlon, K. C., & Brennan, M. F. (2000). Laparoscopy for staging abdominal malignancies. *Advances in Surgery*, *34*, 331-350. https://www.ncbi.nlm.nih.gov/pubmed/10997227

Cook, J. A. (2009). The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. *Trials [Electronic Resource]*, *10*, 9. https://doi.org/10.1186/1745-6215-10-9

Cook, J. A., Elders, A., Boachie, C., Bassinga, T., Fraser, C., Altman, D. G., Boutron, I., Ramsay, C. R., & MacLennan, G. S. (2015). A systematic review of the use of an expertise-based randomised controlled trial design. *Trials [Electronic Resource]*, *16*, 241. https://doi.org/10.1186/s13063-015-0739-5

Cook, J. A., McCulloch, P., Blazeby, J. M., Beard, D. J., Marinac-Dabic, D., Sedrakyan, A., & Group, I. (2013). IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage. *BMJ*, *346*, f2820. https://doi.org/10.1136/bmj.f2820

Cook, J. A., Ramsay, C. R., & Norrie, J. (2008). Recruitment to publicly funded trials--are surgical trials really different? *Contemporary Clinical Trials*, *29*(5), 631-634. https://doi.org/10.1016/j.cct.2008.02.005

D'Alimonte, L., Deabreu, A., Marquez, A., Mamedov, A., & Loblaw, A. (2015). Improving clinical trial accrual through a novel feedback approach: Lessons learned from a single disease site group. *Pract Radiat Oncol*, *5*(2), 70-73. https://doi.org/10.1016/j.prro.2014.05.009

Del Fabro G, B. S., Thoma A, Sprague S. (2019 (avaliable from: https://doi.org/10.1007/978-3-030-05120-4. Springer). Evidence-Based Surgery. A Guide To Understanding and Interpreting the Surgical Literature. 37-44.

Denost, Q., Adam, J. P., Rullier, A., Buscail, E., Laurent, C., & Rullier, E. (2014). Perineal transanal approach: a new standard for laparoscopic sphincter-saving resection in low rectal cancer, a randomized trial. *Ann Surg*, *260*(6), 993-999. https://doi.org/10.1097/SLA.0000000000000766

Devereaux, P. J., Bhandari, M., Clarke, M., Montori, V. M., Cook, D. J., Yusuf, S., Sackett, D. L., Cina, C. S., Walter, S. D., Haynes, B., Schunemann, H. J., Norman, G. R., & Guyatt, G. H. (2005). Need for expertise based randomised controlled trials. *BMJ*, *330*(7482), 88. https://doi.org/10.1136/bmj.330.7482.88

Diehr, P., Cain, K., Ye, Z., & Abdul-Salam, F. (1993). Small area variation analysis. Methods for comparing several diagnosis-related groups. *Med Care*, *31*(5 Suppl), YS45-53. https://www.ncbi.nlm.nih.gov/pubmed/8492585

Donovan, J., Mills, N., Smith, M., Brindle, L., Jacoby, A., Peters, T., Frankel, S., Neal, D., & Hamdy, F. (2002). Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ*, *325*(7367), 766-770. https://doi.org/10.1136/bmj.325.7367.766

Dowrick, A. S., & Bhandari, M. (2012). Ethical issues in the design of randomized trials: to sham or not to sham. *Journal of Bone & Joint Surgery - American Volume*, *94 Suppl 1*, 7-10. https://doi.org/10.2106/JBJS.L.00298

Ellis, J., Mulligan, I., Rowe, J., & Sackett, D. L. (1995). Inpatient general medicine is evidence based. A-Team, Nuffield Department of Clinical Medicine. *Lancet*, *346*(8972), 407-410. https://www.ncbi.nlm.nih.gov/pubmed/7623571

Ergina, P. L., Cook, J. A., Blazeby, J. M., Boutron, I., Clavien, P. A., Reeves, B. C., Seiler, C. M., Balliol, C., Altman, D. G., Aronson, J. K., Barkun, J. S., Campbell, W. B., Cook, J. A., Feldman, L. S., Flum, D. R., Glasziou, P., Maddern, G. J., Marshall, J. C., McCulloch, P., . . . Vandenbroucke, J. (2009). Challenges in evaluating surgical innovation. *Lancet*, *374*(9695), 1097-1104. https://doi.org/10.1016/S0140-6736(09)61086-2

Etchells, E. (1999). Informed consent in surgical trials. *World J Surg*, *23*(12), 1215-1219. https://doi.org/10.1007/s002689900650

Evrard, S., McKelvie-Sebileau, P., van de Velde, C., Nordlinger, B., & Poston, G. (2016). What can we learn from oncology surgical trials? *Nat Rev Clin Oncol*, *13*(1), 55-62. https://doi.org/10.1038/nrclinonc.2015.176

FC, H. Radiation Therapy and Cisplatin With or Without Surgery in Treating Patients With Stage III-IV Oropharyngeal Cancer. *https://clinicaltrials.gov/ct2/show/NCT01953952*, *accessed Apr 12 2021*.

Featherstone, K., & Donovan, J. L. (1998). Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial. *BMJ*, *317*(7167), 1177-1180. https://doi.org/10.1136/bmj.317.7167.1177

Fielding, L. P., Stewart-Brown, S., & Dudley, H. A. (1978). Surgeon-related variables and the clinical trial. *Lancet*, *2*(8093), 778-779. https://doi.org/10.1016/s0140-6736(78)92660-0

Flodgren, G., O'Brien, M. A., Parmelli, E., & Grimshaw, J. M. (2019). Local opinion leaders: effects on professional practice and healthcare outcomes. *Cochrane Database of Systematic Reviews*, *6*, CD000125. https://doi.org/10.1002/14651858.CD000125.pub5

Foy, R., Parry, J., Duggan, A., Delaney, B., Wilson, S., Lewin-Van Den Broek, N. T., Lassen, A., Vickers, L., & Myres, P. (2003). How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. *Fam Pract*, *20*(1), 83-92. https://doi.org/10.1093/fampra/20.1.83

Fretland, A. A., Dagenborg, V. J., Bjornelv, G. M. W., Kazaryan, A. M., Kristiansen, R., Fagerland, M. W., Hausken, J., Tonnessen, T. I., Abildgaard, A., Barkhatov, L., Yaqub, S., Rosok, B. I., Bjornbeth, B. A., Andersen, M. H., Flatmark, K., Aas, E., & Edwin, B. (2018). Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. *Ann Surg*, *267*(2), 199-207. https://doi.org/10.1097/SLA.0000000000002353

Frobell, R. B., Lohmander, L. S., & Roos, E. M. (2007). The challenge of recruiting patients with anterior cruciate ligament injury of the knee into a randomized clinical trial comparing surgical and non-surgical treatment. *Contemporary Clinical Trials*, *28*(3), 295-302. https://doi.org/10.1016/j.cct.2006.10.002

Gelijns, A. C., Ascheim, D. D., Parides, M. K., Kent, K. C., & Moskowitz, A. J. (2009). Randomized trials in surgery. *Surgery*, *145*(6), 581-587. https://doi.org/10.1016/j.surg.2009.04.003

Haidich, A. B., & Ioannidis, J. P. (2001). Patterns of patient enrollment in randomized controlled trials. *J Clin Epidemiol*, *54*(9), 877-883. https://doi.org/10.1016/s0895-4356(01)00353-5

Halpern, S. D., Ubel, P. A., Berlin, J. A., Townsend, R. R., & Asch, D. A. (2002). Physicians' preferences for active-controlled versus placebo-controlled trials of new antihypertensive drugs. *J Gen Intern Med*, *17*(9), 689-695. https://doi.org/10.1046/j.1525-1497.2002.11024.x

Hare, K. B., Lohmander, L. S., & Roos, E. M. (2014). The challenge of recruiting patients into a placebo-controlled surgical trial. *Trials [Electronic Resource]*, *15*, 167. https://doi.org/10.1186/1745-6215-15-167

Harrop, E., Kelly, J., Griffiths, G., Casbard, A., Nelson, A., & Published on behalf of the, B. T. M. G. (2016). Why do patients decline surgical trials? Findings from a qualitative interview study embedded in the Cancer Research UK BOLERO trial (Bladder cancer: Open versus Lapararoscopic or RObotic cystectomy). *Trials [Electronic Resource]*, *17*, 35. https://doi.org/10.1186/s13063-016-1173-z

Hassenpflug, M., Hinz, U., Strobel, O., Volpert, J., Knebel, P., Diener, M. K., Doerr-Harim, C., Werner, J., Hackert, T., & Buchler, M. W. (2016). Teres Ligament Patch Reduces Relevant Morbidity After Distal Pancreatectomy (the DISCOVER Randomized Controlled Trial). *Ann Surg*, *264*(5), 723-730. https://doi.org/10.1097/SLA.0000000000001913

Hawker, G., Guan, J., Judge, A., & Dieppe, P. (2008). Knee arthroscopy in England and Ontario: patterns of use, changes over time, and relationship to total knee replacement. *Journal of Bone & Joint Surgery - American Volume*, *90*(11), 2337-2345. https://doi.org/10.2106/JBJS.G.01671

Haynes RB, S. D., Guyatt GH, Tugwell P. (2006. Lippincott Williams & Wilkins). Clinical Epidemiology. How to do Clinical Practice Research. 224-228.

Homer, C. S. (2002). Using the Zelen design in randomized controlled trials: debates and controversies. *J Adv Nurs*, *38*(2), 200-207. https://doi.org/10.1046/j.1365-2648.2002.02164.x

Horton, R. (1996). Surgical research or comic opera: questions, but few answers. *Lancet*, *347*(9007), 984-985. https://doi.org/10.1016/s0140-6736(96)90137-3

Howes, N., Chagla, L., Thorpe, M., & McCulloch, P. (1997). Surgical practice is evidence based. *Br J Surg*, *84*(9), 1220-1223. https://www.ncbi.nlm.nih.gov/pubmed/9313697

Johnson, A. G., & Dixon, J. M. (1997). Removing bias in surgical trials. *BMJ*, *314*(7085), 916-917. https://doi.org/10.1136/bmj.314.7085.916

Kaas, R., Hart, A. A., & Rutgers, E. J. (2005). The impact of the physician on the accrual to randomized clinical trials in patients with primary operable breast cancer. *Breast*, *14*(4), 310-316. https://doi.org/10.1016/j.breast.2005.01.004

Kan, P., & Kestle, J. R. (2007). Designing randomized clinical trials in pediatric neurosurgery. *Childs Nervous System*, *23*(4), 385-390. https://doi.org/10.1007/s00381-006-0293-2

Keck, T., Wellner, U. F., Bahra, M., Klein, F., Sick, O., Niedergethmann, M., Wilhelm, T. J., Farkas, S. A., Borner, T., Bruns, C., Kleespies, A., Kleeff, J., Mihaljevic, A. L.,

Uhl, W., Chromik, A., Fendrich, V., Heeger, K., Padberg, W., Hecker, A., . . . Hopt, U. T. (2016). Pancreatogastrostomy Versus Pancreatojejunostomy for RECOnstruction After PANCreatoduodenectomy (RECOPANC, DRKS 00000767): Perioperative and Long-term Results of a Multicenter Randomized Controlled Trial. *Ann Surg*, *263*(3), 440-449. https://doi.org/10.1097/SLA.0000000000001240

Kelly, J. R., Park, H. S., An, Y., Contessa, J. N., Yarbrough, W. G., Burtness, B. A., Decker, R., & Husain, Z. (2017). Comparison of Survival Outcomes Among Human Papillomavirus-Negative cT1-2 N1-2b Patients With Oropharyngeal Squamous Cell Cancer Treated With Upfront Surgery vs Definitive Chemoradiation Therapy: An Observational Study. *JAMA Oncol*, *3*(8), 1107-1111. https://doi.org/10.1001/jamaoncol.2016.5769

Kennedy, E. D., Blair, J. E., Ready, R., Wolff, B. G., Steinhart, A. H., Carryer, P. W., & McLeod, R. S. (1998). Patients' perceptions of their participation in a clinical trial for postoperative Crohn's disease. *Can J Gastroenterol*, *12*(4), 287-291. https://doi.org/10.1155/1998/274172

Kost, R. G., Mervin-Blake, S., Hallarn, R., Rathmann, C., Kolb, H. R., Himmelfarb, C. D., D'Agostino, T., Rubinstein, E. P., Dozier, A. M., & Schuff, K. G. (2014). Accrual and recruitment practices at Clinical and Translational Science Award (CTSA) institutions: a call for expectations, expertise, and evaluation. *Acad Med*, *89*(8), 1180-1189. https://doi.org/10.1097/ACM.0000000000000308

Kuroki, L., Stuckey, A., Hirway, P., Raker, C. A., Bandera, C. A., DiSilvestro, P. A., Granai, C. O., Legare, R. D., Sakr, B. J., & Dizon, D. S. (2010). Addressing clinical trials: can the multidisciplinary Tumor Board improve participation? A study from an academic women's cancer program. *Gynecol Oncol*, *116*(3), 295-300. https://doi.org/10.1016/j.ygyno.2009.12.005

Lamont, E. B., Hayreh, D., Pickett, K. E., Dignam, J. J., List, M. A., Stenson, K. M., Haraf, D. J., Brockstein, B. E., Sellergren, S. A., & Vokes, E. E. (2003). Is patient travel distance associated with survival on phase II clinical trials in oncology? *Journal of the National Cancer Institute*, *95*(18), 1370-1375. https://doi.org/10.1093/jnci/djg035

Lasagna, L. (1979). Problems in publication of clinical trial methodology. *Clin Pharmacol Ther*, *25*(5 Pt 2), 751-753. https://doi.org/10.1002/cpt1979255part2751

Lilford, R., Braunholtz, D., Harris, J., & Gill, T. (2004). Trials in surgery. *Br J Surg*, *91*(1), 6-16. https://doi.org/10.1002/bjs.4418

Mackintosh DR, M. V. (2001). Differences in Clinical Trial Conduct in US and EU Investigational Sites. *Qual Assur J*, *5*, 13-17.

Mahon, D., Rhodes, M., Decadt, B., Hindmarsh, A., Lowndes, R., Beckingham, I., Koo, B., & Newcombe, R. G. (2005). Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. *Br J Surg*, *92*(6), 695-699. https://doi.org/10.1002/bjs.4934

Majeed, A. W., Troy, G., Nicholl, J. P., Smythe, A., Reed, M. W., Stoddard, C. J., Peacock, J., & Johnson, A. G. (1996). Randomised, prospective, single-blind comparison of

laparoscopic versus small-incision cholecystectomy. *Lancet*, *347*(9007), 989-994. https://doi.org/10.1016/s0140-6736(96)90143-9

McCulloch, P., Altman, D. G., Campbell, W. B., Flum, D. R., Glasziou, P., Marshall, J. C., Nicholl, J., Balliol, C., Aronson, J. K., Barkun, J. S., Blazeby, J. M., Boutron, I. C., Campbell, W. B., Clavien, P. A., Cook, J. A., Ergina, P. L., Feldman, L. S., Flum, D. R., Maddern, G. J., . . . Vandenbroucke, J. (2009). No surgical innovation without evaluation: the IDEAL recommendations. *Lancet*, *374*(9695), 1105-1112. https://doi.org/10.1016/S0140-6736(09)61116-8

McCulloch, P., Kaul, A., Wagstaff, G. F., & Wheatcroft, J. (2005). Tolerance of uncertainty, extroversion, neuroticism and attitudes to randomized controlled trials among surgeons and physicians. *Br J Surg*, *92*(10), 1293-1297. https://doi.org/10.1002/bjs.4930

McCulloch, P., Taylor, I., Sasako, M., Lovett, B., & Griffin, D. (2002). Randomised trials in surgery: problems and possible solutions. *BMJ*, *324*(7351), 1448-1451. https://doi.org/10.1136/bmj.324.7351.1448

McDonald, A. M., Knight, R. C., Campbell, M. K., Entwistle, V. A., Grant, A. M., Cook, J. A., Elbourne, D. R., Francis, D., Garcia, J., Roberts, I., & Snowdon, C. (2006). What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials [Electronic Resource]*, *7*, 9. https://doi.org/10.1186/1745-6215-7-9

McLeod, R. S. (1999). Issues in surgical randomized controlled trials. *World J Surg*, *23*(12), 1210-1214. https://doi.org/10.1007/s002689900649

McLeod, R. S., Wright, J. G., Solomon, M. J., Hu, X., Walters, B. C., & Lossing, A. (1996). Randomized controlled trials in surgery: Issues and problems. *Surgery*, *119*(5), 483-486. https://doi.org/10.1016/s0039-6060(96)80254-6

Mills, N., Donovan, J. L., Smith, M., Jacoby, A., Neal, D. E., & Hamdy, F. C. (2003). Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. *Control Clin Trials*, *24*(3), 272-282. https://doi.org/10.1016/s0197-2456(03)00020-5

Moseley, J. B., O'Malley, K., Petersen, N. J., Menke, T. J., Brody, B. A., Kuykendall, D. H., Hollingsworth, J. C., Ashton, C. M., & Wray, N. P. (2002). A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *New England Journal of Medicine*, *347*(2), 81-88. https://doi.org/10.1056/NEJMoa013259

Mouw, T. J., Hong, S. W., Sarwar, S., Fondaw, A. E., Walling, A. D., Al-Kasspooles, M., & DiPasco, P. J. (2018). Discontinuation of surgical versus nonsurgical clinical trials: an analysis of 88,498 trials. *J Surg Res*, *227*, 151-157. https://doi.org/10.1016/j.jss.2018.02.039

NIH. (2019 (cited 2020 Nov 27) Available from: https://grants.nih.gov/policy/clinical-trials/definition.htm). NIH Definition of a Clinical Trial. https://grants.nih.gov/policy/clinical-trials/definition.htm

NJ, S. (2004). Clinical Studies: Europe or the United States? *Medical Device and Diagnostic Industry (MDDI)*, *https://www.mddionline.com/print/845*(accessed on April 12 2021).

North American Symptomatic Carotid Endarterectomy Trial, C., Barnett, H. J. M., Taylor, D. W., Haynes, R. B., Sackett, D. L., Peerless, S. J., Ferguson, G. G., Fox, A. J., Rankin, R. N., Hachinski, V. C., Wiebers, D. O., & Eliasziw, M. (1991). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine*, *325*(7), 445-453. https://doi.org/10.1056/NEJM199108153250701

Prescott, R. J., Counsell, C. E., Gillespie, W. J., Grant, A. M., Russell, I. T., Kiauka, S., Colthart, I. R., Ross, S., Shepherd, S. M., & Russell, D. (1999). Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol Assess*, *3*(20), 1-143. https://www.ncbi.nlm.nih.gov/pubmed/10683591

Robinson, N. B., Fremes, S., Hameed, I., Rahouma, M., Weidenmann, V., Demetres, M., Morsi, M., Soletti, G., Di Franco, A., Zenati, M. A., Raja, S. G., Moher, D., Bakaeen, F., Chikwe, J., Bhatt, D. L., Kurlansky, P., Girardi, L. N., & Gaudino, M. (2021). Characteristics of Randomized Clinical Trials in Surgery From 2008 to 2020: A Systematic Review. *JAMA Netw Open*, *4*(6), e2114494. https://doi.org/10.1001/jamanetworkopen.2021.14494

Rose, E. A., Gelijns, A. C., Moskowitz, A. J., Heitjan, D. F., Stevenson, L. W., Dembitsky, W., Long, J. W., Ascheim, D. D., Tierney, A. R., Levitan, R. G., Watson, J. T., Meier, P., Ronan, N. S., Shapiro, P. A., Lazar, R. M., Miller, L. W., Gupta, L., Frazier, O. H., Desvigne-Nickens, P., . . . Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure Study, G. (2001). Long-term use of a left ventricular assist device for end-stage heart failure. *New England Journal of Medicine*, *345*(20), 1435-1443. https://doi.org/10.1056/NEJMoa012175

Rosenthal, R., Kasenda, B., Dell-Kuster, S., von Elm, E., You, J., Blumle, A., Tomonaga, Y., Saccilotto, R., Amstutz, A., Bengough, T., Meerpohl, J. J., Stegert, M., Tikkinen, K. A., Neumann, I., Carrasco-Labra, A., Faulhaber, M., Mulla, S., Mertz, D., Akl, E. A., . . . Briel, M. (2015). Completion and Publication Rates of Randomized Controlled Trials in Surgery: An Empirical Study. *Ann Surg*, *262*(1), 68-73. https://doi.org/10.1097/SLA.0000000000000810

Ross, S., Grant, A., Counsell, C., Gillespie, W., Russell, I., & Prescott, R. (1999). Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol*, *52*(12), 1143-1156. https://doi.org/10.1016/s0895-4356(99)00141-9

Serrano, P. E., Bhandari, M., & Simunovic, M. (2021). Surgical Culture Shifts and Randomized Clinical Trials. *JAMA Netw Open*, *4*(6), e2115456. https://doi.org/10.1001/jamanetworkopen.2021.15456

Serrano, P. E., Gafni, A., Parpia, S., Ruo, L., Simunovic, M., Meyers, B. M., Reiter, H., Wei, A., Gallinger, S., Karanicolas, P., Hallet, J., Devaud, N., & Levine, M. (2018). Simultaneous resection of colorectal cancer with synchronous liver metastases (RESECT), a pilot study. *Int J Surg Protoc*, *8*, 1-6. https://doi.org/10.1016/j.isjp.2018.01.001

Sibai, T., Carlisle, H., & Tornetta, P., 3rd. (2012). The darker side of randomized trials: recruitment challenges. *Journal of Bone & Joint Surgery - American Volume*, *94 Suppl 1*, 49-55. https://doi.org/10.2106/JBJS.L.00240

Siminoff, L. A., Zhang, A., Colabianchi, N., Sturm, C. M., & Shen, Q. (2000). Factors that predict the referral of breast cancer patients onto clinical trials by their surgeons and medical oncologists. *J Clin Oncol*, *18*(6), 1203-1211. https://doi.org/10.1200/JCO.2000.18.6.1203

Solomon, M. J., & McLeod, R. S. (1993). Clinical studies in surgical journals--have we improved? *Diseases of the Colon & Rectum*, *36*(1), 43-48. https://doi.org/10.1007/BF02050300

Solomon, M. J., & McLeod, R. S. (1998). Surgery and the randomised controlled trial: past, present and future. *Medical Journal of Australia*, *169*(7), 380-383. https://www.ncbi.nlm.nih.gov/pubmed/9803252

Stirrat, G. M., Farrow, S. C., Farndon, J., & Dwyer, N. (1992). The challenge of evaluating surgical procedures. *Ann R Coll Surg Engl*, *74*(2), 80-84. https://www.ncbi.nlm.nih.gov/pubmed/1567147

Surgical research: the reality and the IDEAL. (2009). *Lancet*, *374*(9695), 1037. https://doi.org/10.1016/S0140-6736(09)61678-0

Taylor, K. M., Margolese, R. G., & Soskolne, C. L. (1984). Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. *New England Journal of Medicine*, *310*(21), 1363-1367. https://doi.org/10.1056/NEJM198405243102106

Thoma, A., Farrokhyar, F., McKnight, L., & Bhandari, M. (2010). Practical tips for surgical research: how to optimize patient recruitment. *Can J Surg*, *53*(3), 205-210. https://www.ncbi.nlm.nih.gov/pubmed/20507795

Treweek, S., Lockhart, P., Pitkethly, M., Cook, J. A., Kjeldstrom, M., Johansen, M., Taskila, T. K., Sullivan, F. M., Wilson, S., Jackson, C., Jones, R., & Mitchell, E. D. (2013). Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open*, *3*(2). https://doi.org/10.1136/bmjopen-2012-002360

van der Linden, W. (1980). Pitfalls in randomized surgical trials. *Surgery*, *87*(3), 258-262. https://www.ncbi.nlm.nih.gov/pubmed/6987765

van Hilst, J., de Rooij, T., Bosscha, K., Brinkman, D. J., van Dieren, S., Dijkgraaf, M. G., Gerhards, M. F., de Hingh, I. H., Karsten, T. M., Lips, D. J., Luyer, M. D., Busch, O. R., Festen, S., Besselink, M. G., & Dutch Pancreatic Cancer, G. (2019). Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *Lancet Gastroenterol Hepatol*, *4*(3), 199-207. https://doi.org/10.1016/S2468-1253(19)30004-4

Wallace, K., Fleshner, N., Jewett, M., Basiuk, J., & Crook, J. (2006). Impact of a multi-disciplinary patient education session on accrual to a difficult clinical trial: the Toronto experience with the surgical prostatectomy versus interstitial radiation intervention trial. *J Clin Oncol*, *24*(25), 4158-4162. https://doi.org/10.1200/JCO.2006.06.3875

Wang, J., Serrano, P. E., Griffiths, C., Parpia, S., & Simunovic, M. (2020). Enthusiasm, Opinion Leaders, Comparative Advantage, and the Uptake Of Laparoscopic Resection For Colorectal Cancer Liver Metastases in Ontario, Canada: A

Population-Based Cohort Study. *Ann Surg Oncol*. https://doi.org/10.1245/s10434-020-09203-0

Wartolowska, K., Collins, G. S., Hopewell, S., Judge, A., Dean, B. J., Rombach, I., Beard, D. J., & Carr, A. J. (2016). Feasibility of surgical randomised controlled trials with a placebo arm: a systematic review. *BMJ Open*, *6*(3), e010194. https://doi.org/10.1136/bmjopen-2015-010194

Wente, M. N., Seiler, C. M., Uhl, W., & Buchler, M. W. (2003). Perspectives of evidence-based surgery. *Digestive Surgery*, *20*(4), 263-269. https://doi.org/10.1159/000071183

Whitlock, R. P., Belley-Cote, E. P., Paparella, D., Healey, J. S., Brady, K., Sharma, M., Reents, W., Budera, P., Baddour, A. J., Fila, P., Devereaux, P. J., Bogachev-Prokophiev, A., Boening, A., Teoh, K. H. T., Tagarakis, G. I., Slaughter, M. S., Royse, A. G., McGuinness, S., Alings, M., . . . Investigators, L. I. (2021). Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. *New England Journal of Medicine*, *384*(22), 2081-2091. https://doi.org/10.1056/NEJMoa2101897

Zelen, M. (1979). A new design for randomized clinical trials. *New England Journal of Medicine*, *300*(22), 1242-1245. https://doi.org/10.1056/NEJM197905313002203

Chapter 2.

Perioperative Optimization with Nutritional Supplements in Patients Undergoing Gastrointestinal Surgery for Cancer: A Randomized, Placebo Controlled Feasibility Clinical Trial.

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INTRODUCTION TO CHAPTER 2

This chapter describes the feasibility of a surgical clinical trial comparing perioperative nutritional supplements to placebo among patients undergoing gastrointestinal cancer surgery. Based on the framework described in the Introduction of this thesis (Chapter 1), this study fell into the first category of surgical clinical trials, a trial that investigates medical therapies among surgical patients. This trial was chosen because this is the most common type of surgical clinical trial performed currently (~65%).

There are certain limitations and difficulties in the recruitment process that are unique to trials that investigate medical therapies among surgical patients. Specifically for this trial, recruitment, randomization and administration of the intervention or placebo must happen several weeks prior to surgery, which is not a typical issue for surgical trials that investigate a surgical intervention. Having to identify, randomize and administer the intervention or placebo several weeks prior to surgery makes the recruitment of potential participants difficult. Enrolling cancer surgical patients to a trial four weeks prior to their scheduled surgery is complex. Surgeries are frequently scheduled within two to four weeks of patient's first encounter with the surgeon (date of the decision to operate) and this date often changes to an earlier or a later date depending on operating room availability. Coordination between the research team and the surgeon must be very precise to avoid missing a potential participant.

Different strategies or opportunities to improve recruitment are provided throughout the chapter and a summary is provided at the end of the chapter.

Perioperative Optimization with Nutritional Supplements in Patients Undergoing Gastrointestinal Surgery for Cancer: A Randomized, Placebo Controlled Feasibility Clinical Trial.

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Brief Title: Trial of perioperative nutritional supplement

ABSTRACT

Background

Perioperative nutritional supplementation may improve outcomes. Trials have not investigated the role of combination strategy using different types of nutritional supplements.

Study Design

We conducted a single-site randomized pilot trial, among gastrointestinal cancer patients undergoing surgery, comparing perioperative nutritional supplements versus placebo (one placebo to each supplement), to determine feasibility of a larger trial. Intervention, administered in sequence, included: protein supplementation (preoperative day 30-6), protein supplementation rich in arginine and omega-6 (preoperative day 5-1 and postoperative day 1-5), and carbohydrate loading (surgery day). Primary outcome was enrollment. Secondary outcomes included participant compliance with study supplements (target ≥70% of total packets). We planned protocol modifications to improve enrollment and compliance. Postoperative complications were described.

Results

Over 18 months, 495 patients were screened, 144 were deemed eligible, and 71 consented to participate, resulting in an enrollment fraction of 71/144 (49%, 95% CI 41%-57%). 'Too much burden' was the most common reason for refusal to participate (34%). Participants' median overall compliance with study packets was 80%. Protocol modifications (decreasing the interval from enrollment to surgery from 4 to 2 weeks and decreasing length of baseline assessment) did not impact enrollment or compliance. Postoperative

complications were similar between control (18/31 (58%, 95% CI: 41-74)) and intervention (22/34 (65%, 95% CI 48-79)) arms, with a higher proportion of infectious complications in the control arm (16/31, 52% versus 12/34, 35%).

Conclusion

Results from this pilot suggest a larger phase III trial is feasible. Postoperative infectious complications were common, making this a suitable outcome of interest.

INTRODUCTION

Perioperative nutritional supplements in patients with gastrointestinal cancer undergoing surgery, may decrease postoperative complications and length of hospital stay.[1] However, the optimal duration, route of administration, and type of nutrients in the formulations have not been well defined. It is thought that perioperative oral supplementation of protein, solutions rich in arginine, omega-6 fatty acids, and solutions high in glucose taken the day of surgery (carbohydrate loading), while working separately through different mechanisms of action, are associated with better postoperative outcomes.[2-4]

Patients undergoing surgery experience a degree of immunosuppression characterized by an intensification of the lymphocyte T helper type 2 (Th2) over the Th1 cell response and a suppression of the cellular immunity, in particular, natural killer cell function.[5, 6] This reported shift may be one of the factors increasing the susceptibility to infections and septic complications following surgery.[7] Oral supplementation of arginine, omega-6 fatty acids and nucleotides may modulate the immune system, as they are necessary elements for normal T cell function.[8] These supplements have the potential to modulate the activity of the immune system and thus decrease postoperative infectious complications. [9]

Patients undergoing surgery experience an extended period of insulin resistance that can last 3 to 4 weeks after surgery.[10] This state of postoperative insulin resistance is related to the increased release of cortisol and glucagon associated with surgical stress, which induce gluconeogenesis, glycogenolysis and decreased glucose uptake in peripheral tissues,

stimulating a high degree of catabolism.[11] The practice of administering a large amount of carbohydrates before surgery is called "carbohydrate loading" and it is intended to allow maximal glycogen storage, a metabolically "fed state" at the time of surgery, and decreased insulin resistance, although the mechanism of action for the latter is not fully understood.[11, 12] Decreasing insulin resistance following surgery has been associated with lower rates of postoperative complications and has been adopted by different surgical society guidelines.[13]

We believe that a combination of these three interventions (administered in sequence), including 1) perioperative nutritional supplements with protein-rich solutions, 2) protein rich solutions with omega-6 fatty acids, nucleotides, and arginine supplementation (i.e., immunonutrition), and 3) carbohydrate loading prior to surgery; can have an additive effect to improve postoperative outcomes. A phase III trial testing the efficacy of these three different types of perioperative nutritional supplements versus placebo will require a large sample size and considerable resources. The main purpose of this study was to identify potential factors that may arise as obstacles to the trial successful execution as those factors would need to be overcome. Therefore, we performed a single-centre, placebo-controlled, pilot randomized clinical trial, to determine the feasibility of such a phase III trial. Our primary goal was to evaluate rate of enrollment and participants' compliance with perioperative nutritional supplements. Secondary outcomes included postoperative infectious complications and other postoperative complications, the logical primary endpoints of a larger phase III randomized trial.

MATERIALS AND METHODS

Study Design and Setting

This was a parallel, 1:1, placebo-controlled, double-blinded, feasibility randomized clinical trial at a single tertiary care academic hospital in Ontario, Canada. The randomization scheduled was web-based, computer-generated and stratified by nutritional risk status, using the Malnutrition Universal Screening Tool (MUST).[14]. The interventions and placebo were produced and provided at a cost by Enhanced Medical Nutrition, Toronto, Canada. All supplements were sent directly to the Pharmacy Research Support Services, located in the trial institution (i.e., pharmacy). Data were unblinded after statistical analyses were performed.

Participants

Potentially eligible patients for the trial included consecutive adult patients that presented with a resectable type of gastrointestinal cancer for which an elective operation was planned.[15] Patients were excluded from eligibility if they had type 1 diabetes, malabsorption syndrome, end organ failure, inflammatory diseases, galactosemia or ongoing infections, poorly controlled type 2 diabetes mellitus, were on systemic steroids, unable to tolerate oral intake, pregnant, or lactating females, surgery scheduled in less than 4 weeks. Eligible patients were approached to be enrolled once we obtained confirmation from their surgeon(s) that an operation would take place. Reasons for non-enrollment were collected in anonymized case report forms. This trial was registered with clinicaltrials.gov (NCT03445260) and approved by the Institutional Research Ethics Board prior to initiation. All patients provided written informed consent prior to enrollment.

Study Intervention

Patients received perioperative nutritional supplements or placebo. This study used a commercial immune nutrition and protein supplement designed based on the recommendations of ASPEN and ESPEN.[16, 17] The intervention consisted of the following three different solutions: 1) a protein isolate powder (ISOlution®, Enhanced Medical Nutrition, Toronto, Canada) containing 20g of protein. Patients were instructed to consume 1 serving per day mixed with either liquid or soft food, from the time of randomization until 6 days before surgery (from "day -30" to "day -6" of surgery). 2) An "immunonutrition" solution (Inergy-FLD®, Enhanced Medical Nutrition, Toronto, Canada) containing arginine, protein isolate, omega-6 fatty acids, and RNA (51g of powder reconstituted in 250mL of cold water). Patients were asked to consume 3 servings per day for 5 days prior to surgery (from "day -5" to "day -1" of surgery) and for 5 days following surgery (from "day 1" to "day 5" after surgery). If patients were discharged home prior to postoperative day 5, they were asked to take the supplements home and continue taking them until they were finished. 3) Carbohydrate-rich solution (PreCovery®, Enhanced Medical Nutrition, Toronto, Canada) containing 50g of maltodextrin at a 12.5% carbohydrate concentration, including 2g of glucides. This carbohydrate loading solution was reconstituted in 400 mL of cold water and was administered 2 servings the evening before surgery and 1 serving 2-3 hours before anaesthesia. Each of the solutions administered to patients in the intervention arm had a similar placebo. The placebo looked exactly as the intervention externally (packet) and internally (white powder). Each placebo

was composed of a collagen-based filler (zero calories) with the same taste and texture as the intervention.

Following randomization, patients waited in the clinic for study package to be given to them by the pharmacy; this process was revised in January 2019 as the time to wait was approximately 90 minutes and some patients were not willing to enroll in the trial when they were informed that they might have to wait long for the trial package, and they were expressing that they were feeling overwhelmed already. After January 2019, patients went home after they consented and the intervention or the placebo package was mailed to them via an overnight courier service (blinded package). Postoperative supplements initially were administered by patients themselves, however, this was changed in March 2019 so that the clinical nurses taking care of patients administered the packets as a type of medication, and recorded patient's compliance in their nurses' computer log.

Outcomes

The primary outcome was enrollment. This was measured as an enrollment fraction, defined as number of enrolled patients / numbers of eligible patients. A priori, we decided the trial would be feasible if the enrollment fraction, was $\geq$40%. Also, if the ongoing observed enrollment fraction was between 40-59%, we would allow protocol modifications to optimize the chances of an enrollment fraction $\geq$40%. An enrollment fraction of $\geq$60% would be considered excellent and would not require any protocol modifications during the pilot phase. Secondary outcomes included: 1) patients' compliance with study packets: defined as "good" if intake was at least 70% of study supplements. The number of packets each patient had to take varied according to the number of days prior to surgery that each

patient was randomized, from a maximum of 58 packets to a minimum of 42 packets. 2) Overall complications: occurrence of any postoperative complication from surgery up to 90 days from the index operation according to the Clavien-Dindo classification (CD), and the Comprehensive Complication Index.[18, 19] 3) Rate of any infectious complications at 90 days from surgery, 4) health related quality of life (QoL) measured using the EORTC-QLQ-C30 instrument [20] and the FACT-G scale[21] at 30 and 90 days from surgery. 5) Length of hospital stay 6) Eligibility fraction, defined as the number of eligible patients / number of patients meeting inclusion criteria (i.e., potentially eligible patients). 7) Recruitment fraction, defined as the number of enrolled patients / number of patients meeting inclusion criteria (i.e., potentially eligible patients).

Eligibility, Follow-up, and Data Collection

Patients seen in the outpatient surgical clinics with no exclusion criteria and with a confirmed operative date within a minimum of 4 weeks, were approached for informed consent and enrollment. This requirement was modified to a minimum of 2 weeks in March 2019, to facilitate enrollment, after a review of the literature suggested no major differences between 2 or 4 weeks of preoperative supplementation.[22]

During the initial clinic visit, patients underwent a baseline assessment that included QoL questionnaires and baseline demographics. Patients were asked to fill a compliance diary daily (paper or electronic) and reasons for non-compliance were collected. Patients were called 5 days prior to their operation to remind them they had to change the type of supplement they were taking and to encourage compliance.

Postoperative complication data up to 90 days following surgery (including procedural re-interventions or re-operations and hospital re-admissions or emergency room visits) were collected.

Statistical Analyses

Sample size was based around the precision of the proportion of eligible patient being enrolled. With an estimated 18-month duration of the study, and 300 potentially eligible patients (i.e., patients meeting inclusion criteria), we expected at least 165 (55%) patients to be eligible for the study. We anticipated that 60% (n=100) of the eligible patients were going to be enrolled (enrollment fraction), giving us a 95% confidence interval (CI) around the estimate of 53% to 68%. In March 2020, due to government mandated changes to research activity related to the COVID-19 pandemic, the steering committee performed an interim blinded data analysis of the primary outcome (enrollment fraction) and decided, based on the available results, the stable trajectory of enrollment rate throughout the trial, and assuming the same trend of enrollment would continue, that a larger sample size would not be able to show a higher enrollment rate and therefore, it would not change the results of the trial. Therefore, it was decided to stop the trial early with the sample size of 71.

Patient baseline characteristics were presented using descriptive statistics. Categorical variables were presented in number and percentage and continuous variables as median and interquartile range (IQR), as appropriate. Compliance was calculated for each patient individually by dividing the number of study packets consumed by the number of study packets they were assigned. Compliance was presented as proportion of patients adhering to >50% and >70% of study packets. Overall compliance with study packets was

presented as median and IQR. Overall, major, and infectious postoperative complications were presented as the proportion with 95% CI, calculated using the Wilson-Score method. Overall complications were also expressed as the median and IQR of the comprehensive complication index. QoL outcomes were summarized using means and corresponding standard deviations (SD). A change in the mean score of 10% or more was defined as a minimal clinical important difference.[23, 24] Statistical analyses were performed using R (R Foundation for Statistical Computing, version 3.5.0, Vienna, Austria).

RESULTS

Patient Flow and Feasibility Outcome Measure

Between October 2018 and March 2020, 495 patients met the inclusion criteria and were deemed potentially eligible participants, of which, 174 met an exclusion criterion (see consort diagram in Figure 1). There were 177 patients that did not meet an exclusion criterion but were not asked to be enrolled and therefore were "not eligible" due to short interval between identification as a potentially eligible participant and surgery (eligibility fraction: 29% (144/495), 95% CI, 25-33). Of the remaining 144 eligible participants, 71 agreed to participate in the study (primary outcome, enrollment fraction 49%, 95% CI 41-57).

The proportion of participants enrolled remained 51nchangedd throughout the duration of the study, without any difference in the proportion of participants randomized before or after the decision to enroll with interval to surgery ≤2 weeks. However, the decision to allow the interval to surgery to be ≤2 weeks significantly increased the number

of participants eligible for the trial, improving the eligibility fraction (Figure 2). The eligibility fraction increased from 18%, 95% CI, 12-27 before March 2019 to 34%, 95% CI, 30-39 after March 2019. Reasons for non-enrollment were: 25/73 (34%) patients felt overwhelmed, 10/73 (14%) patients did not agree with the placebo arm, and 5/73 (7%) patients had their own nutritional support. There were 33/73 (45%) patients that did not provide a reason for refusing to participate. The recruitment fraction was 14% (71/495), 95% CI, 12-18. Median number of days patients were enrolled prior to surgery differed between groups: control: 15 days (IQR, 10-25) and intervention: 24 days (IQR, 15-30) (Table 1).

Participant baseline characteristics

Baseline characteristics of participants are described in Table 1. However, the location of the tumour and the type of surgery participants underwent were not balanced between arms, with a lower proportion of participants with pancreatic tumours randomized to the control group (3/35, 9%) compared to the intervention group (13/36, 36%).

Patients' Compliance with Study Packets

Compliance with study packets was similar between groups, however, compliance with the postoperative solution was higher in the placebo group (Table 2). Median overall participants' compliance with all supplements for both groups was 80% (IQR, 20-100) Median compliance did not change throughout the study period nor did it change based on the number of preoperative days participants were required to ingest the packets. The most common reason for non-compliance with the postoperative solution in the placebo versus the intervention group were related to nausea (57% vs. 73%, respectively).

Clinical Outcomes

In the control and intervention group, respectively, the proportion of participants experiencing infectious complications was 52% (16/31), 95% CI, 35-68% and 35% (12/34), 95% CI, 22-52% (Table 3). The most common postoperative infectious complications were intra-abdominal abscess (26% versus 21%), pneumonia (16% versus 3%), and wound infection (19% versus 12%) (Supplementary Table 1). Postoperative chemotherapy was administered to 6/31 (19%) participants (control group) and 9/34 (27%) participants (intervention group). The median number of days from surgery to chemotherapy was 70 (IQR, 40-139) in the control and 60 (IQR, 54-90) in the intervention group. Postoperative weight and biochemical nutritional assessment are reported in Supplementary Table 2.

Of enrolled participants, overall compliance with all QoL questionnaires was 66/97 (68%) in the control group and 67/104 (64%) in the intervention group. At 4 weeks from surgery, the decline from baseline in most scores was lower in the intervention group compared to control, with no difference in scores between groups. At 12 weeks from surgery, most EORTC-QLQ-C30 and FACT-G domains returned to baseline levels in the intervention, however not in the control group (Supplementary Figure 1a, 1b and 1c).

DISCUSSION

Enrolling patients with gastrointestinal cancer to a randomized placebo-controlled trial of perioperative nutritional supplements is feasible according to our pre-specified enrollment fraction criteria. Enrollment fraction remained stable throughout the trial duration, despite protocol modifications. Although enrollment fraction was within a pre-

specified acceptable limit, the number of patients needed to screen in order to accrue one patient was higher than anticipated, therefore, the eligibility fraction and recruitment fraction were lower than expected (29% and 14%, respectively).[25]

One protocol modification made during the trial, aimed to increase the enrollment fraction, was to allow a decrease in the interval from enrollment to surgery from 4 to 2 weeks. We noticed that there were many screened patients (177/495, 36%) that were being categorized as "not eligible" and therefore excluded, due to a short time interval to surgery. We considered that by increasing the number of eligible participants, we could increase the proportion of participants enrolled. Our results show, that although the number of eligible participants substantially increased immediately after the implementation of this protocol modification, the proportion of participants being enrolled remained the same. Moreover, the reasons for not being enrolled were similar. Based on the feedback from patients that refused to participate due to the feeling of being overwhelmed, we implemented another protocol modification early on. Some patients were not willing to enroll to the trial when we explained that they had to wait 90 minutes for the supplements to be given to them by the pharmacy. With the change, we allowed participants to go home after randomization, and the supplements and QoL questionnaires were couriered to them overnight. We strongly believed that this change increased the enrollment rate in February and March 2019. However, when analyzing the proportion of participants being enrolled throughout the trial, we do not see a significant difference after these protocol changes. In response to the high number of patients who refused to participate due to the feeling of being overwhelmed by trial procedures, some of the modifications that could be implemented to

increase enrollment include: 1) limiting the first encounter with patient to a maximum of 15 minutes (i.e., only do the informed consent), performing the rest of the baseline assessment at a later meeting over the phone, 2) eliminate the use of self-compliance diaries given the high compliance found with preoperative supplements. The assessment of compliance can be performed through simpler self-reported assessments the day of surgery,[26] 3) decrease the number of QoL questionnaires administered and to find better timing for participants to fill them out (i.e., using either the EORTC-QLQ-C30 *or* the FACT-G questionnaire in the preoperative unit, while they wait for their surgery).

Participants' compliance with the preoperative packets was good, however, specific compliance with the postoperative supplements in both groups was poor. For that reason, we involved the ward nurses to administer the intervention or placebo to participants and to keep record of their intake as part of their regular medication log. This process improved the record keeping of the compliance and the reasons for participants not taking the supplements, however, it did not improve participants' compliance with study packets. Compliance with the postoperative solution was much lower in the intervention group compared to control, which led to differences in overall compliance between groups. This was related to the higher proportion of participants in the intervention group undergoing pancreatectomies (35% vs. 7%), patients that are known to have a high rate of delayed gastric emptying and nausea.[27]

Postoperative infectious complications were common in both arms. There was a trend for lower infectious complications in the intervention group compared to control, particularly pneumonia, which would make the outcome of infectious complications a good

candidate for a primary outcome in future studies. The intervention and control group had different baseline scores in most QoL domains, which could be related to the imbalance in the types of tumours among patients. It is known that patients with pancreatic malignancies have low QoL scores even prior to surgery.[28] However, the decline in most QoL domains was substantially worse in the control group compared to the intervention group (i.e., more participants meeting the minimal clinical important difference threshold), suggesting a signal that is worth exploring further. This trend in QoL was better appreciated with the FACT-G domains, making this questionnaire the preferred tool for this patient population.

We showed that it is feasible to enrol participants in a placebo-controlled trial of combination perioperative nutritional supplements with a high rate of compliance with study packets and QoL questionnaires. Adherence to study procedures, including participants follow-up was excellent. There are some limitations to our study that are worth discussing. Although it is unlikely that the enrollment rate would have changed if the initially proposed sample size of 100 patients would have been achieved, it is possible that some of the changes proposed herein would have taken place and would have provided information on potential influence on enrollment. The unbalanced proportion of participants undergoing pancreatic surgery between groups makes it challenging to determine if differences between groups are related to the intervention or placebo or to differences in patients baseline characteristics. To prevent imbalances between arms for known factors that influence response to the intervention, a future trial should stratify randomization according to the type of tumour participants have (pancreatic versus other). Since none of the protocol changes implemented demonstrated a substantial improvement

in the enrollment fraction during the trial, it is reasonable to accept a 50% enrollment rate as the threshold to which a future larger trial must be planned. It is important to understand that 50% enrollment fraction is good, especially considering that most trials enrol between 30% to 35% of eligible patients.[25, 29] By anticipating an enrollment fraction in a larger trial of 50%, we can then inform plans for sample size, budget, timelines, number of sites, etc. The feasibility of this trial may not be modifiable at the patient level, but rather at the level of trial procedures such as those described above.

CHALLENGES AND OPPORTUNITIES FOR IMPROVEMENT

This chapter reported the results of a pilot study demonstrating the feasibility of a large randomized controlled trial comparing three different perioperative nutritional supplements to placebo among patients with gastrointestinal cancer undergoing surgery.

Throughout the duration of the trial, we encountered different areas that could be explored to improve the recruitment process (Table 4).

1) Study population: the main challenge for this study was the need to enroll and randomize patients four weeks prior to surgery. This is difficult, as often surgeons and / or patients do not know the date of the operation, and this date is subject to change. Moreover, patients with cancer commonly have surgery within two to four weeks of diagnosis, decreasing their chances of being eligible for clinical trials prior to surgery. One opportunity to improve recruitment is to identify patients early in their cancer journey (i.e., prior to their first clinic visit with the surgeon or when their case is being first discussed at multidisciplinary rounds). Once the patient attends the surgical clinics, the research staff is already aware of them due to previous discussions with surgeons

and can discuss with the patient the possible trials they would be eligible for. This first encounter will establish a relationship between the research personnel and potential new participants. Patients and surgeons' administrative staff will be asked to notify the research team as soon as they know a date for surgery. Also, research staff will follow up with surgeon's administrative staff and potential participant, at one and three weeks from the first visit to determine if a patient will undergo surgery within 4 weeks. Once a plan for surgery has been confirmed, even if it has not yet been booked, the research team will call the potential participant to invite them to participate in the study, that had been previously described to them. There are some disadvantages with this method, and they must be considered. By approaching all potential participants without confirming if they will have surgery, the workload for the research team will be higher, which may not be feasible when the research team is small and already "stretched out" to their maximum capacity. Secondly, patients may not wish to hear potential research options when they are unaware if they require surgery. Thirdly, there may not be enough physical space in the surgical clinics to spend time with multiple potential participants.

2) Study intervention: the intervention or control needed to be administered for four weeks prior to surgery, which is a challenge as explained above. Given that there is no data on the length of preoperative nutritional supplements that are required, we were able to amend the protocol to administer the intervention / control for 2 weeks prior to surgery. This increased the number of eligible patients to the study.
3) Blinding methods: Some patients were not interested in the study due to blinding. They considered that they would not want to be in the study if they were taking placebo and

that they would rather take nutritional supplements on their own. The opportunity here is for the research staff to do their best to explain to patients the concept of clinical equipoise and to emphasize that the surgical community does not know if a combination of different nutritional supplements would improve outcomes after surgery and attempt to incentivise patients this way.

4) Statistical considerations: there were 5% of patients (same in both arms) that were enrolled to the study and later their surgery was cancelled due to progression of disease (i.e., cancer). Having learned this in the pilot study, we will add 5% of patients to each arm when considering the sample size.
5) Ethical and regulatory standards (i.e., consent process): many patients were not keen to be randomized because the consent process and baseline assessment was too long. We believe a shorter baseline interview to obtain consent and essential baseline assessment questions (max 15 min) will improve recruitment. Baseline assessment can be finished later over the phone or at a different clinic visit.
6) Timing of the trial: no issues
7) Standardization of the surgical intervention: no issues
8) Patient preferences: some patients believe that taking nutritional supplements around the time of surgery is important and are not willing to be randomized to a placebo arm. The opportunity here is to explain to all patients that they will be coached by a dietitian prior to surgery to recommend dietary changes they can all make prior to surgery so that everyone has an opportunity to improve their nutritional support, therefore the

placebo arm will not only include a placebo but also an assessment and recommendations by dietitians, which is standard of care in many institutions already.

9) Surgeon preferences: no issues
10) Referring physician preferences: no issues
11) Funding: no issues

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DISCLOSURE STATEMENT

All authors report no conflict of interest.

References

1. Zhang B, Najarali Z, Ruo L, Alhusaini A, Solis N, Valencia M, et al. Effect of Perioperative Nutritional Supplementation on Postoperative Complications-Systematic Review and Meta-Analysis. J Gastrointest Surg. 2019;23:1682-93.
2. Hamza N, Darwish A, O'Reilly DA, Denton J, Sheen AJ, Chang D, et al. Perioperative enteral immunonutrition modulates systemic and mucosal immunity and the inflammatory response in patients with periampullary cancer scheduled for pancreaticoduodenectomy: a randomized clinical trial. Pancreas. 2015;44:41-52.
3. Horie H, Okada M, Kojima M, Nagai H. Favorable effects of preoperative enteral immunonutrition on a surgical site infection in patients with colorectal cancer without malnutrition. Surgery today. 2006;36:1063-8.
4. Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab. 2001;280:E576-83.
5. Dabrowska AM, Slotwinski R. The immune response to surgery and infection. Cent Eur J Immunol. 2014;39:532-7.
6. Angka L, Khan ST, Kilgour MK, Xu R, Kennedy MA, Auer RC. Dysfunctional Natural Killer Cells in the Aftermath of Cancer Surgery. Int J Mol Sci. 2017;18.
7. Suzuki D, Furukawa K, Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, et al. Effects of perioperative immunonutrition on cell-mediated immunity, T helper type 1 (Th1)/Th2 differentiation, and Th17 response after pancreaticoduodenectomy. Surgery. 2010;148:573-81.
8. Zhu X, Herrera G, Ochoa JB. Immunosupression and infection after major surgery: a nutritional deficiency. Crit Care Clin. 2010;26:491-500, ix.
9. Calder PC. Immunonutrition. Bmj. 2003;327:117-8.
10. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care. 1999;2:69-78.
11. Gillis C, Carli F. Promoting Perioperative Metabolic and Nutritional Care. Anesthesiology. 2015;123:1455-72.
12. Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand. 2015;59:1212-31.
13. Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. The British journal of surgery. 2014;101:1209-29.
14. M E. Screening for malnutrition: a multi-disciplinary responsibility. Development and use of the "Malnutrition Universal Screening Tool" ("MUST") for adults. MAG, a Standing Committee of BAPEN. 2003;ISBN: 1 899467 70 X.
15. Serrano PE, Parpia S, Nair S, Ruo L, Simunovic M, Levine O, et al. Perioperative Optimization With Nutritional Supplements in Patients Undergoing Gastrointestinal Surgery for Cancer (PROGRESS): Protocol for a Feasibility Randomized Controlled Trial. JMIR Res Protoc. 2018;7:e10491.

16. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40:159-211.
17. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr. 2017;36:623-50.
18. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240:205.
19. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013;258:1-7.
20. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85:365-76.
21. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of clinical oncology. 1993;11:570-9.
22. Borloni B, Huettner H, Schuerholz T. Preoperative Nutritional Conditioning: Why, When and How. Visc Med. 2019;35:299-304.
23. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16:139-44.
24. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. Cancer. 2007;110:196-202.
25. Wright JR, Bouma S, Dayes I, Sussman J, Simunovic MR, Levine MN, et al. The importance of reporting patient recruitment details in phase III trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24:843-5.
26. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67-74.
27. Glowka TR, Webler M, Matthaei H, Schafer N, Schmitz V, Kalff JC, et al. Delayed gastric emptying following pancreatoduodenectomy with alimentary reconstruction according to Roux-en-Y or Billroth-II. BMC surg. 2017;17:24.
28. Serrano PE, Herman JM, Griffith KA, Zalupski MM, Kim EJ, Bekaii-Saab TS, et al. Quality of life in a prospective, multicenter phase 2 trial of neoadjuvant full-dose gemcitabine, oxaliplatin, and radiation in patients with resectable or borderline resectable pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2014;90:270-7.
29. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol. 1999;52:1143-56.

Figure 1: Patient Flow – Consort Diagram. Patients meeting inclusion criteria: screened patients. Eligible patients: patients meeting eligibility criteria.

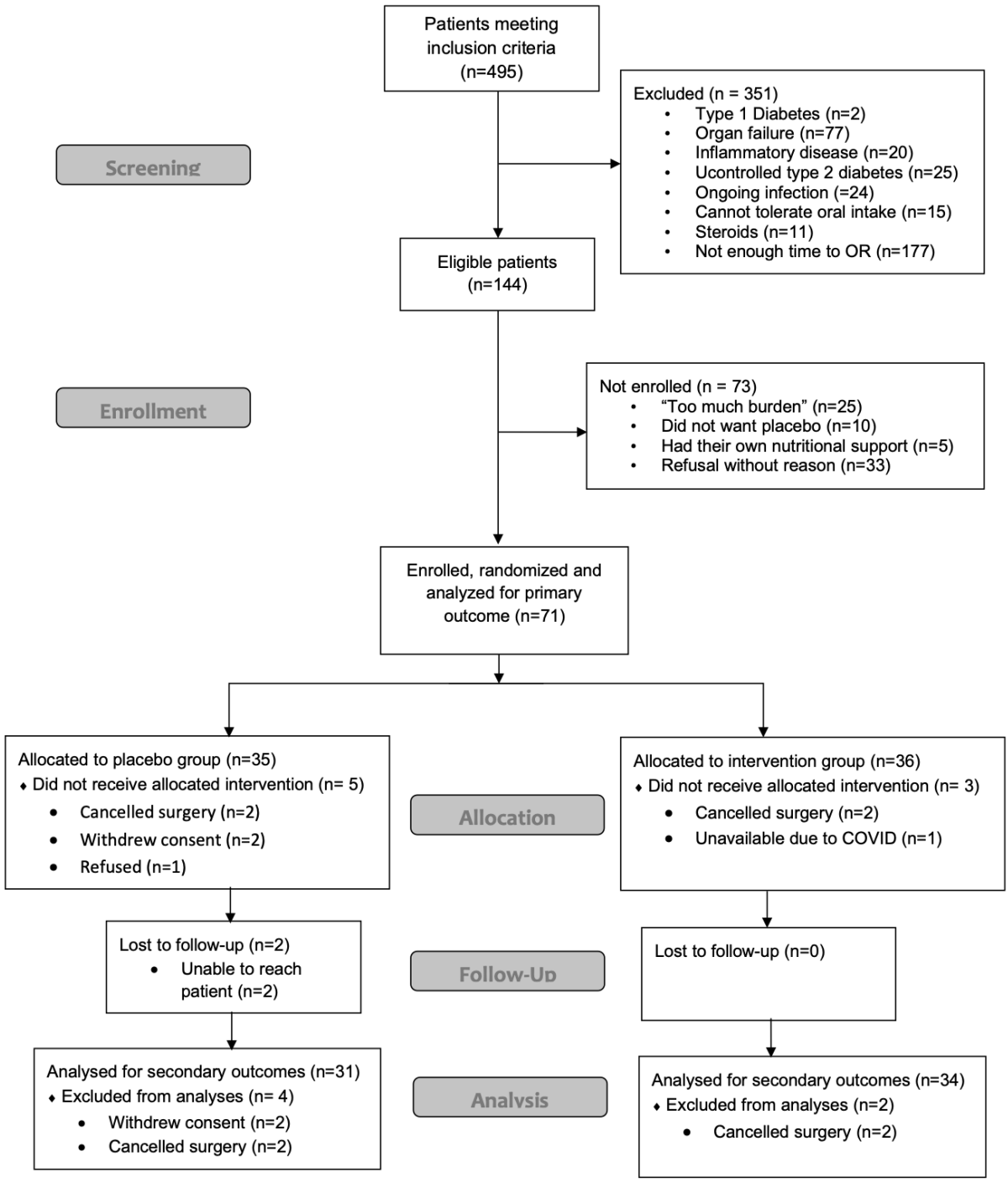


Figure 2. Proportion of Enrolled Patients Throughout Trial Duration

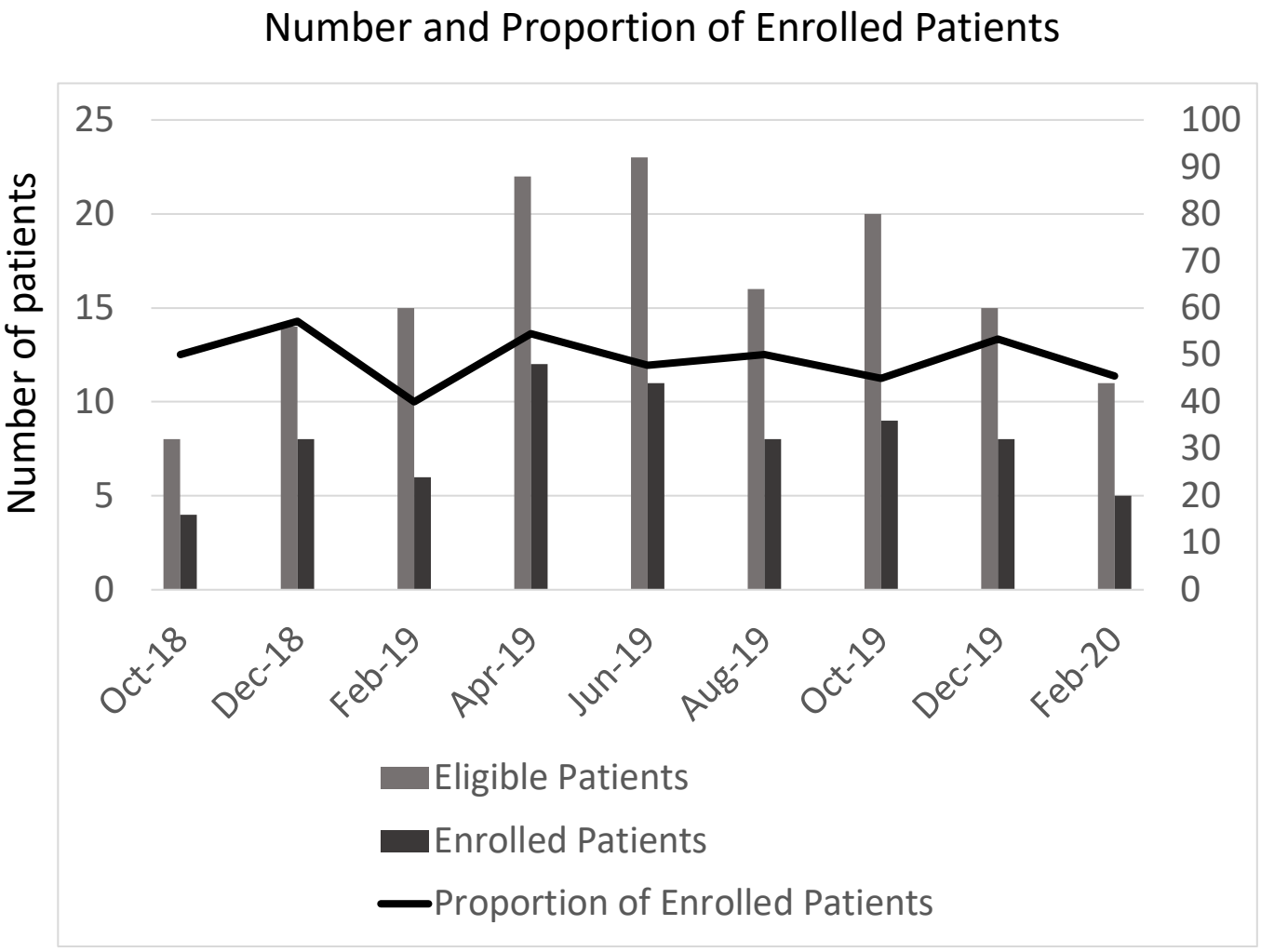


Table 1. Baseline patient characteristics. ASA: American Society of Anesthesiologists. IQR: interquartile range. BMI: Body Mass Index.

Variable	Placebo n= 35	Intervention n= 36
Age median (IQR)	63 (59 to 68)	65 (59 to 72)
Female Sex n (%)	15 (43%)	14 (39%)
Risk of Malnutrition n (%)		
Medium / high risk	12 (36%)	13 (36%)
Weight (Kg) median IQR	80 (72 to 95)	85 (71 to 91)
BMI (Kg/m2) median IQR	29 (25 to 31)	30 (35 to 33)
Tumour location n (%)		
Liver	16 (46%)	15 (42%)
Pancreas	3 (9%)	13 (36%)
Colorectal	12 (34%)	7 (19%)
ASA Class n (%)		
ASA 4	25 (71%)	24 (67%)
Resection Type n (%)		
Colorectal resection	12 (39%)	7 (21%)
Hepatectomy	13 (42%)	15 (44%)
Pancreatectomy	2 (7%)	12 (35%)
Days enrolled prior to surgery median (IQR)	15 (10 to 25)	24 (15 to 30)

Table 2. Patient's compliance with intervention and placebo. IQR: interquartile range

TYPE OF SOLUTION	Placebo COMPLIANCE	Intervention COMPLIANCE	ALL PATIENTS
Preoperative solution (Day -30 to -6) Median (IQR)	95% (49 to 100)	92% (62 to 100)	93% (50 to 100)
Preoperative solution (Day -5 to -1) Median (IQR)	100% (63 to 100)	87% (27 to 100)	90% (33 to 100)
Day of surgery solution (Day 0) Median (IQR)	67% (0 to 100)	67% (0 to 100)	67% (0 to 100)
Postoperative solution (Day 1 to 5) Median (IQR)	50% (7 to 72)	23% (0 to 35)	27% (0 to 60)
All solutions combined (Overall) Median (IQR)	87% (23 to 100)	67% (20 to 100)	80% (20 to 100)

Table 3. Postoperative outcomes**.** IQR: interquartile range. ER: Emergency Room. CI: confidence interval. CCI: Comprehensive Complication Index.

Outcomes	Placebo n=31	Intervention n=34
Length of Stay (median, IQR) [days]	6 (3 to 9)	6 (5 to 10)
Unplanned visit to ER n (%, 95% CI)	11 (36%, 21 to 53%)	11 (32%, 19 to 49%)
Readmission n (%, 95% CI)	8 (26%, 14 to 43%)	4 (12%, 5 to 27%)
All postoperative morbidity (Clavien-Dindo Grade 1 to 5) n (%, 95% CI)	18 (58%, 41 to 74%)	22 (65%, 48 to 79)
Major postoperative morbidity (Clavien-Dindo Grade ≥3) n (%, 95% CI)	8 (26%, 14 to 43%)	8 (24%, 12 to 40%)
Infectious complications n (%, 95% CI)	16 (52%, 35 to 68%)	12 (35%, 22 to 52%)
90-day mortality n (%, 95% CI)	2 (7%, 2 to 21%)	3 (9%, 3 to 23%)
CCI median (median, IQR)	29 (21 to 39)	25 (21 to 33)

Table 4. Challenges and opportunities for improvement in the PROGRESS trial.

Variable	Challenge	Opportunity
Study population	Not enough time to enroll patients prior to surgery	Approach patients at their first clinic visit with surgeon
Study intervention	Administration for 4 weeks prior to surgery	Administration for 2 weeks prior to surgery
Blinding methods	Patients not willing to be randomized to placebo	Explain importance clinical equipoise
Statistical considerations	Proportion of randomized patients not undergoing surgery	Adjust sample size based on the findings of the pilot study
Ethical and regulatory standards	Baseline assessment including consent was too long	Baseline assessment to include only patient consent
Timing of the trial	NA	NA
Standardization	NA	NA
Patient preference	Patients' beliefs in the importance of nutritional supplements	Offer dietitian advice to both arms
Surgeon preference	NA	NA
Referring physician preference	NA	NA
Funding	NA	NA

Supplement Table 1: Postoperative Bloodwork and Weight. IQR: interquartile range. BMI: Body Mass Index.

Variable	Placebo n=31	Intervention n=34
Creatinine µmol/L median (IQR)		
3 days	63 (59 to 74)	64 (56 to 71)
5 days	63 (57 to 68)	63 (56 to 67)
4 weeks	69 (64 to 73)	70 (64 to 84)
Albumin g/L median (IQR)		
3 days	27 (23 to 30)	27 (23 to 28)
5 days	23 (21 to 28)	25 (24 to 28)
4 weeks	29 (27 to 31)	28 (27 to 33)
Glucose mmol/L median (IQR)		
3 days	6 (5.5 to 6.4)	7 (6.1 to 8.7)
5 days	5.8 (5.1 to 7.4)	6.3 (5.6 to 8.4)
4 weeks	6.9 (6.3 to 9.2)	8.8 (6.8 to 10.1)
Weight Kg median (IQR)		
4 weeks	79 (75 to 90)	78 (67 to 88)
12 weeks	80 (68 to 94)	82 (75 to 92)
BMI (Kg/m2) median IQR		
4 weeks	27 (23 to 32)	28 (23 to 30)
12 weeks	29 (26 to 32)	29 (26 to 33)

Supplement Table 2: Types of Postoperative Complications

Event	**Placebo n=31**	**Intervention n=34**
Intra-abdominal abscess	8 (26%)	7 (21%)
Bacteremia	1 (3%)	2 (6%)
Pneumonia	5 (16%)	1 (3%)
Wound infection	6 (19%)	4 (12%)
Urinary tract infection	-	2 (6%)
Organ failure	3 (10%)	2 (6%)
Small bowel obstruction	1 (3%)	2 (6%)

Supplementary Figure 1: Quality of life. Figure 1a: EORTC-QLQ-C30, Figure 1b: FACT-G Gastrointestinal Cancer Subscale, Figure 1c FACT-G Total Outcome Index.

Figure 1a.

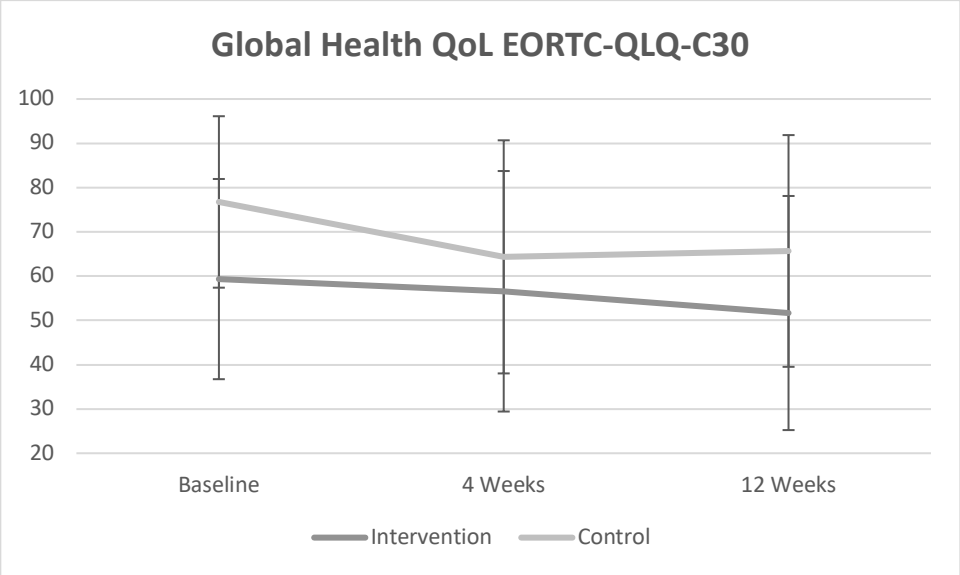


Figure 1b.

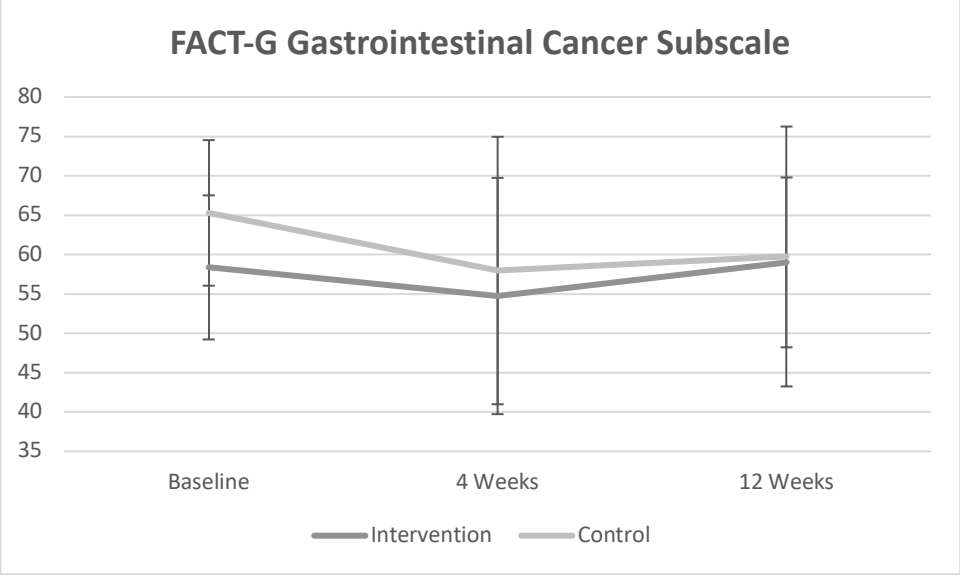
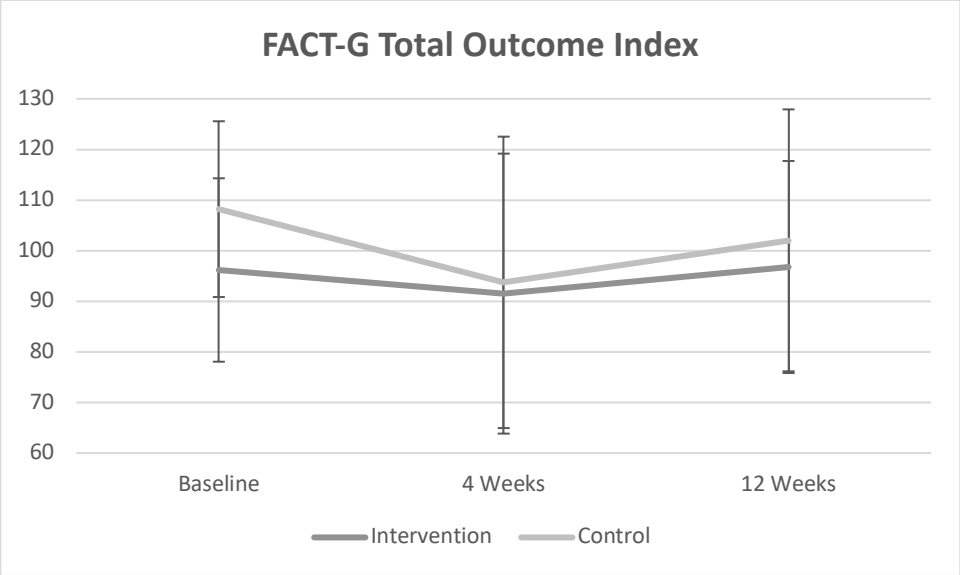


Figure 1c.


FACT-G Total Outcome Index
130
120
110
100
90
80
70
60
Baseline
4 Weeks
12 Weeks
Intervention
Control

Chapter 3.

Simultaneous resection for synchronous colorectal cancer liver metastases: a feasibility clinical trial.

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Introduction to Chapter 3

In this chapter, we examined the feasibility of a trial for a surgical intervention that was in its earlier stages of evaluation, the exploration phase. This study falls into the second category of surgical clinical trials, a trial that investigates surgical interventions, specifically, a trial that would compare different ways to perform an operation, involving significant differences, such as the overall approach and skills. By the time this trial was developed, there were many retrospective reviews published, however no prospective surgical trials had been performed. Therefore, after careful consideration and after obtaining support from different surgical groups, we decided to perform a single arm trial to evaluate the feasibility of performing simultaneous resection and to capture data systematically for every patient undergoing the procedure, specifically to ensure that all eligible patients were accounted for and that adverse outcomes were documented.

Although not a randomized trial, this study offers the opportunity to evaluate most recruitment issues that were developed in chapter 1 of this thesis as it is a "typical" surgical trial. These issues and the opportunities for improvement are developed at the end of the chapter only.

Simultaneous resection for synchronous colorectal cancer liver metastases: a feasibility clinical trial.

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Running Head: simultaneous resection feasibility trial

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SYPNOPSIS

- We performed a feasibility trial of simultaneous colorectal cancer liver metastasectomy
- Pre-specified feasibility criteria: ≥66% enrollment of eligible patients and ≥75% completion of simultaneous resection
- Trial is feasible; however, it is associated with higher than anticipated 90-day postoperative complications (41%)

ABSTRACT

Background and Objectives

We tested the feasibility of a simultaneous resection clinical trial in patients with synchronous colorectal cancer liver metastases to obtain the necessary information to plan a randomized trial.

Methods

Multi-centre feasibility single arm trial enrolling patients with synchronous colorectal cancer liver metastases eligible for simultaneous resection. Pre-specified criteria for feasibility were: proportion of eligible patients enrolled ≥66% and, proportion of enrolled patients who completed simultaneous resection ≥75%. Pre-specified 90-day major postoperative complication rate was 30%.

Results

Of 61 eligible patients from February 2017 to August 2019, 41 were enrolled (67%, 95% confidence interval (CI), 55-78%), 32 underwent simultaneous resection (78%, 95% CI, 63-88%). Four patients were not enrolled due to surgeon's preference, 3 due to complexity of resection (right hepatectomy and low anterior resection). Intraoperative complications during liver resection (n=4) and progression of disease (n=4) were the main reasons for not undergoing simultaneous resection. The 90-day incidence of major complications was 41% (95% CI, 16-58%) and the 90-day postoperative mortality was 6% (95% CI, 1.7-20%).

Conclusion

According to pre-specified criteria, enrolling patients with synchronous colorectal cancer liver metastases to a trial of simultaneous resection is feasible, however it is associated with higher than anticipated 90-day postoperative complications.

Keywords: Colorectal Cancer, Colorectal Liver metastases, synchronous metastases, simultaneous resection, clinical trial**,** feasibility**.**

1. BACKGROUND

Approximately 25% of patients who are diagnosed with colon cancer have synchronous liver metastases.[1-3] These patients with synchronous disease may still be candidates for cure by resecting the primary tumour and the liver metastases with or without the addition of systemic chemotherapy.[4,5] Patients able to undergo complete margin-negative resection are anticipated to have a 5-year overall survival of 50%.[6,7]

The appropriate timing of liver and colorectal resection among patients who present with synchronous disease has not been standardized. Most patients undergo the more traditional staged resection pathway (i.e., resection of the primary and liver metastases on separate admissions with a period of recovery between the two operations), while others undergo simultaneous resection (i.e., resection of the primary and liver metastases on the same operative day). Simultaneous resection is an attractive option as it decreases the number of operations a patient will need, it may have an overall shorter length of hospital stay and thus lower health care costs, and it may avoid disease progression while waiting for a second surgery. However, staged resections may have lower rates of postoperative complications. Finally, a delay to liver surgery may demonstrate aggressive disease that avoids what would have proven to be a futile liver resection.

The decision to proceed with a simultaneous versus a staged approach is complex and depends on multiple factors, such as, location of the primary tumour, extent of liver metastases, patient comorbidities, availability of HPB surgeons and local practice. Most studies informing the decision for simultaneous versus staged resections are retrospective and observational, and many are from single centres. Thus, there is great potential for bias

favouring lower risk patients who undergo simultaneous resection, or possibly favouring patients who undergo delayed liver resection after demonstrating slow-growing disease. The only way to resolve such uncertainty is evidence from well-designed and executed randomized clinical trials. The only randomized controlled trial to date comparing simultaneous versus staged resections was recently published. [8] This multi-centre French trial enrolled 105 patients, of which, 85 were analyzed, and suggested a similar postoperative complication rate between groups (49% versus 46%, respectively), with a trend towards improved disease-free survival and overall survival in the simultaneous group that did not reach statistical significance. However, the trial was long (over 10 years to accrue) and included a small number of patients. Even in the absence of high-quality evidence, the use of simultaneous resection is increasing.[9-11]

We performed a pilot single arm feasibility trial of simultaneous resection. Our primary aim was to determine potential enrollment numbers, rate of enrollment, and rate of simultaneous resection. Results, including potential clinical outcomes, will inform the design of a randomized trial comparing staged versus simultaneous resection.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was a prospective single-arm feasibility trial at three hepato-pancreato-biliary (HPB) centres in Ontario, Canada, involving 11 HPB and 12 colorectal surgeons. Ontario is Canada's largest province (population 15 million) that has centralized high volume centres performing liver resection. Of the 10 dedicated HPB centres that perform liver resections, these three centres perform 50% of liver resections in the province.

2.2 Participants

Potentially eligible patients for the study included adult consecutive patients that presented with a resectable primary colorectal cancer and resectable synchronous liver metastases.[12] Patients were excluded from potential eligibility if they had extrahepatic disease (other than resectable lung metastases), planned primary treatment with local transanal excision, liver metastases resection requiring a two-stage liver procedure, prior liver resection, or if the patient was pregnant. Patients were also excluded if they required resection of more than one additional pelvic or abdominal organ involved by direct primary tumour extension (i.e., duodenum, pancreas, bladder, prostate, or gynecological organs). If patients required neoadjuvant chemotherapy or radiation therapy, they were assessed for study eligibility after the planned neoadjuvant treatment was completed.

Eligible patients were approached to be enrolled once their surgeon(s) decided that a simultaneous resection was possible, however surgeon decision was not a requirement to meet eligibility criteria. The Research Ethics Board at each participating institution approved this study. All patients provided written informed consent prior to enrolment. This feasibility trial was registered with clinicaltrials.gov (NCT02954913).

2.3 Study Intervention

Patients underwent resection of the primary tumour and liver metastases in the same anesthetic setting by one or two different surgeons (i.e., colorectal surgeon and HPB surgeon). The treating physician decided the type of colorectal and liver resection. The type of liver resection was described according to the Couinaud classification and the Brisbane terminology of liver anatomy.[13,14] Resections of 3 or more segments of the liver were

considered a major liver resection.[15] The anesthetic technique and the order of liver resection or colorectal resection was determined by the clinical standard at each institution. It was recommended that a low central venous pressure be maintained in order to decrease intraoperative blood loss [16,17] and that liver resection be performed prior to colorectal resection in order to keep a low central venous pressure during that part of the case. Any deviation from the intended intervention (i.e., colorectal or liver resection not performed at the same time of the index operation) was noted with a reason.

2.4 Surgery, follow up and Data collection

Patients attending the outpatient HPB clinics were screened for potential eligibility using the inclusion criteria. During the clinic visit, potentially eligible patients that did not meet any exclusion criteria were considered eligible patients for the trial. Patients that were eligible for participation were identified and approached for enrollment after confirming with the treating surgeon (s) that a simultaneous approach was possible at the next clinic visit. Following study enrolment, patients underwent a baseline assessment that included Quality of Life (QoL) questionnaires. Patients were then assessed the day of their surgery, every day during their hospital stay, at their first post-operative clinic visit, 4 weeks (± 1 week) and at 12 weeks (± 2 weeks) following the index operation. QoL questionnaire and health resource utilization forms were collected in each postoperative assessment. Operative data (i.e., surgical technique, type of colorectal and liver resection, operative time and estimated blood loss for each procedure), pathological details and, postoperative complication data up to 90 days following surgery (including procedural re-interventions or re-operations and hospital re-admissions or emergency room visits) were collected into

case report forms that included de-identified source documentation and sent to the Coordinating Methods Centre in Hamilton, Ontario. Five-year overall survival information, obtained from Provincial Registries (Institute for Clinical and Evaluative Sciences), was a pre-specified outcome to be obtained without active patient follow-up.

2.5 Outcomes

The goal was to gauge the feasibility of a future randomized controlled trial. Feasibility, the primary outcome was established by pre-defined criteria: 66% of eligible patients enrolled (enrolment fraction) and the proportion of patients who completed simultaneous resection of at least 75%.[18] Baseline characteristics (including location of primary tumour and extent of metastases) of enrolled patients would be analyzed to define the inclusion / exclusion criteria of a larger trial. Secondary clinical outcomes included incidence of major postoperative complications up to 90 days following surgery, which were classified as per Clavien-Dindo (CD) and the Comprehensive Complication Index.[19,20] Although not a component of the feasibility criteria, prior to study start-up, the steering committee agreed that a major complication rate of 30% would be the highest rate accepted for patients undergoing simultaneous resection for synchronous disease, a relative risk increase of 50% (from the baseline rate of 20% obtained from the literature).[8,15,21,22] Other secondary outcomes included health related QoL using the EORTC-QLQ-C30 and the EORTC-QLQ-LMC21. [23,24]

2.6 Statistical Analyses

Sample size was based around the precision of the proportion of eligible patient being enrolled. Assuming an estimated enrolment of 66%, we would require 60 eligible

patients to yield a 95% confidence interval (CI) of 54 to 77 around the estimated enrolment percentage. This would require more than 40 patients to be enrolled. Patient baseline characteristics and demographics, including operative characteristics were presented using descriptive statistics. Categorical variables were presented in number and percentage and continuous variables as median and interquartile range (IQR), as appropriate. The proportion with 95% CI of overall and major postoperative complications and the mortality at 90 days were calculated using the Wilson-Score method. QoL outcomes were summarized using means and corresponding standard deviations (SD). A change in the mean score of 10% or more was defined as a minimal clinical important difference (10-point difference in both scales).[25,26] Statistical analyses were performed using R (R Foundation for Statistical Computing, version 3.5.0, Vienna, Austria).

3. RESULTS

3.1.Patient Demographics

The median age at the time of enrolment was 57 (IQR, 50-67). The most common location of the primary tumour was the rectum in 18/41 (44%) patients, followed by the right (12/41, 29%) and left (11/41, 27%) colon. The median number of liver lesions on imaging was 2 (IQR, 1-3) with 17/41 (42%) patients having bilateral liver lesions. Preoperative chemotherapy was administered to 27/41 (68%) patients (categorized as palliative chemotherapy in 9/41, 22%), with a median number of cycles of 6 (IQR, 5-8) (Table 1). All enrolled patients completed the follow-up schedule.

3.2.Patient Flow and Feasibility Outcome Measure

From February 2017 to August 2019, there were 82 patients who met the inclusion criteria and were deemed potentially eligible patients, of which, 21 met an exclusion criterion, leaving 61 eligible patients (eligibility fraction 74%, 61/82). Of those, 41 (67%, 95% CI 55-78%) were enrolled (enrolment fraction, primary feasibility outcome). The reasons for non-enrollment were: 8 patients were not approached with enough time prior to surgery, 5 patients refused to participate, 4 patients not being enrolled due to surgeon's choice (3 due to complexity of the resection (i.e., right hepatectomy and low anterior resection) and one due to patient's factors (i.e., obesity), and 3 patients had an urgent primary tumour resection after being deemed eligible. The recruitment fraction was 50% (41/82). Of the 41 patients enrolled, 40 patients underwent surgery (1 patient had a lethal preoperative stroke) and 32 underwent simultaneous resection (secondary feasibility outcome: 78%, 95% CI, 63-88%). Reasons for not proceeding with simultaneous resection were: two patients not undergoing surgical resection (exploratory laparotomy / laparoscopy only) due to progression of metastatic disease found at the time of surgery; one patient undergoing liver-only resection due to intraoperative complications leading to death; two patients undergoing colon-only resection due to intraoperative findings of extrahepatic metastatic disease; and three patients undergoing staged resections due to intraoperative complications during liver resection (i.e., bleeding). The median time to staged resection in those three patients was 14 weeks (range 12 to 16) (Figure 1).

3.3. Clinical Outcomes

Among patients who underwent simultaneous resection, the most commonly performed liver resection was a wedge non-anatomical resection (one or multiple wedges) in 10/32 (31%) patients followed by left lateral sectionectomy in 8/32 (25%) patients and right hemihepatectomy in 6/32 (19%) patients. The wedge resection were of the following segments: segment 2 (n=1), segment 7 (n=2), segment 6 (n=1), segment 8 (n=2), multiple segments (n=4). The most commonly performed colorectal resection was a low anterior resection in 14/32 (44%) patients, followed by right hemicolectomy in 10/32 (31%) patients (Table 2). On pathology report, the positive margin rate (i.e., R1 - less or equal to 1mm) was 9/32 (28%), mostly driven by the liver specimen (7/32, 23% - all 7 margins ranging from 0.1 to 0.9 mm). There were no R2 resections performed.

Major postoperative complications (CD ≥3) occurred in 16/40 (39%, 95% CI, 26-54%) patients among those who underwent surgery, and in 13/32 (41%, 95% CI, 26-58%) patients undergoing simultaneous resection (Table 3 and Supplementary Table 1). Respectively, the non-operative re-intervention rate was 14/40 (35%, 95% CI, 22-51%) and 13/32 (41%, 95% CI, 26-58%), the operative re-intervention rate was 3/40 (8%, 95% CI, 2.6-20%) and 3/32 (9%, 95% CI, 3-24%), and the postoperative mortality rate was 4/40 (10%, 95% CI, 4-23%) and 2/32 (6%, 95% CI, 1.7-20%). The postoperative causes of death were: progression of cancer (patient did not undergo resection), postoperative bleeding (patient underwent liver only resection), and for those who underwent simultaneous resection: post-hepatectomy liver failure and colonic anastomotic dehiscence.

Of enrolled patients, there were 39/41 (95%) patients who completed the baseline QoL assessments, 35/38 (92%) the first postoperative assessment and 33/36 (92%) the second postoperative assessment. Of the patients who underwent simultaneous resection, 26/32, 81% completed all planned QoL questionnaires.

There was a decline in the mean global health QoL (EORTC-QLQ-C30) from baseline (mean 68, SD 24.8) to the one-month (mean 62, SD 23, difference: -6.02) and three-month evaluation (mean 64, SD 20, difference: -3.48). The physical functioning score had a clinically significant decline from baseline (mean 86, SD 17) to the one-month evaluation (mean 72, SD 24, difference: -13.97), which recovered at three months (mean 83, SD 18, difference: -3.19), whereas role functioning declined from baseline (mean 76, SD 30) to the one-month evaluation (mean 52, SD 33, difference: -23.68) and did not recovered at three months (mean 56, SD 32, difference: -19.39). Social functioning declined from baseline (mean 78, SD 23) to the one-month (mean 67, SD 30, difference: -10.96) and three-month evaluation (mean 67, SD 27, difference: -10.96). The EORTC-QLQ-LMC-21 identified that fatigue remained an important symptom that did not improve from baseline (mean 33, SD 26) to the one-month and the three-month evaluation (mean difference: -12.12 and -14.24, respectively).

4. DISCUSSION

This study found that enrolling patients with synchronous colorectal cancer liver metastases to a trial of simultaneous resection is feasible, according to the pre-specified enrolment fraction criteria and the proportion of enrolled patients undergoing simultaneous resection. Of the eligible patients, there were only five (5/61, 8%) patients that refused

participation, four (4/61, 7%) that were not enrolled due to surgeon's choice and three patients (3/61, 5%) due to logistical reasons (primary tumour resected urgently elsewhere).

One of the goals of this study was to identify the patient population that surgeons would feel comfortable including in a randomized trial comparing simultaneous to staged liver resections. There were three eligible patients that were not enrolled due to the complexity of resection (i.e., right hepatectomy and low anterior resection) and of the patients enrolled there was only one that underwent a right hepatectomy simultaneous with low anterior resection. These findings suggest that patients who require a right hepatectomy and low anterior resection, may not be favoured to participate in a trial including simultaneous resection. Although we collected the reasons for not enrolling patients that were eligible for the study, we did not collect information on patients that had their primary tumour removed prior to assessment of their liver metastases. Since patients were enrolled at tertiary care referral centres, it is possible that there were many other patients that would have been eligible for simultaneous resection if their primary were still in-situ at the time of assessment, which may have made the enrolment fraction lower and the patient population different (i.e., older patients, more complex resections). In this study, there were three patients undergoing wedge resection of segment 2 or segment 6 combined with a rectal resection or a left colectomy. This may be another patient population not suitable for a randomized trial (i.e., patients that require simple wedge resection of the liver, as surgeons may think that the added morbidity to any colorectal resection would be minimal.

While not defined as a limiting factor to determine feasibility, patients undergoing simultaneous resection experienced a higher than anticipated rate of major postoperative

complications. Although this finding can seem disturbing, a recently published randomized trial comparing simultaneous to staged resections for colorectal cancer liver metastases found a major postoperative complication rate of 41% in the simultaneous group, suggesting similar patient population between studies and implying that the rate of 20% obtained from previous studies was inaccurate.[8] It is our belief that this rate although high, is still in the acceptable range for a complex procedure like this one, especially considering that the postoperative mortality rate, although higher compared to the mortality observed following liver resection alone (3-5%),[27] is similar to previously reported series of simultaneous resection.[3,28] It is also reassuring that even though many QoL domains decreased significantly one month after surgery, most recovered to baseline levels by three months, consistent with previously published work on QoL in patients undergoing liver resection for colorectal cancer metastases.[29] This is especially valid, considering the high compliance rate, suggesting that our QoL results did not overestimate the true QoL.

Some of the limitations of this study include its relatively small sample size, which decreases our ability to make generalizable conclusions, such as predictors of postoperative complications and mortality following surgery, although that was not the purpose of this feasibility trial. It is not clear with this study if patients undergoing complex rectal and liver resections experienced significantly worse postoperative complications compared to those who undergo less complex resections (i.e., left lateral sectionectomy and right hemicolectomy). Those analyses would have provided the surgeon a clearer picture when deciding to enrol patients in a simultaneous versus staged randomized trial. Most importantly, given that this was not a pilot randomized study, we did not answer the

question of whether surgeons and patients were willing to enrol in a randomized trial of simultaneous versus staged resection. At the beginning of this study, we wanted to confirm that surgeons were capable of enrolling patients, and that patients were willing to enrol in a simultaneous resection study, as the idea of this type of resection was relatively new and not fully embraced by the surgical community. With that in mind, we kept a record of patients that were eligible but not enrolled, including reasons for not being enrolled and found only 5 patients who refused to participate in this trial. The recently published randomized trial from Europe may give us a glimpse of the struggles of including patients in such trial, since it took more than 10 years to enrol 85 patients.[8] They cite the difficulty of finding eligible patients in tertiary care institutions since most resectable cases would be resected outside of the HPB centre prior to referral. This situation may also be the case in our region as suggested by prior surgeon surveys in our area; however, the current study was not designed to prove that hypothesis.[30] Moreover, this study is not able to answer the question of whether simultaneous resection of certain cases has already become standard of care. We do not know if surgeons would be willing to randomize a patient to a trial comparing simultaneous versus staged resection if the surgical community as a whole believes that a simple liver resection (i.e., wedge of the left lateral sector) should be performed at the same time as a simple colon resection (i.e., right hemicolectomy).

5. CONCLUSIONS

It is feasible for surgeons to enrol patients in a trial of simultaneous resection for synchronous colorectal cancer liver metastases, however, surgeons may not be willing to enrol patients requiring complex procedures such as right hepatectomy and low anterior

resection. Patients undergoing simultaneous resection have a high rate of postoperative complications, although this is not an impediment for a trial as the postoperative mortality rate is low and the decline in QoL seen at one month from surgery is transient, with most domains returning to back to baseline at three months from surgery. Results from this study will be used to build upon a larger randomized trial comparing simultaneous to staged resections, providing relevant information that can be used to determine patient population, calculate sample size, and define outcomes of interest.

6. CHALLENGES AND OPPORTUNITIES FOR IMPROVEMENT

This chapter reported the results of a pilot study aimed to demonstrate the feasibility of a trial of simultaneous resection for colorectal cancer liver metastases. The goal is to design a large randomized controlled trial of simultaneous versus staged resection for these patients.

Throughout the duration of the trial, we encountered different areas of opportunity that could improve the recruitment process (Table 4).

6.1 ***Study population***: patients requiring complex liver and colorectal surgery are considered to be inadequate candidates for simultaneous resection given hesitancy from surgeons to enroll those patients in this trial. Given this hesitancy, those patients will be excluded from the future larger trial.

6.2 ***Study intervention***: in this trial, the study intervention included a surgical innovation (i.e., a new or modified surgical procedure that differs from currently accepted local practice, the outcomes of which have not been described, and which may entail risk to the patient).[31] Specifically, this intervention would

compare different ways to perform an operation, involving significant differences such as the overall approach and skills (i.e., difficulty Level 2 as described in the Introduction of this thesis).[32] This intervention is therefore a challenging one, as it requires approval from surgeons, patients, and hospitals. One approach to improve recruitment is to emphasize to the potential participant and to the participating surgeons, the importance of the trial, to explain that it has the potential to be practice changing. Also, to explain that previous studies have demonstrated that such intervention is safe and that the main goal of the trial is to investigate other potential benefits of the intervention (i.e., overall survival).

6.3 ***Blinding methods***: since this study was not randomized, blinding is not an issue, however, when planning a randomized trial of this intervention (compared to staged resection or control), there are some issues to consider. Given the complexities of the study intervention, it is not possible to blind the surgeon, the patient or even the outcome assessors. However, it will be possible to blind statisticians for the primary outcome. The lack of blinding should not have an impact over recruitment from the patient perspective as the control or standard of care, is also a type of intervention (i.e., staged resection) and would not involve a placebo arm.

6.4 ***Statistical considerations***: there were ~20% of patients that were enrolled to the study and were not able to undergo simultaneous resection. The reasons were varied, from surgical complications to progression of metastatic disease. Having

learned this in the pilot study, we will add 20% of patients to each arm when considering the sample size of a randomized trial.

6.5 ***Ethical and regulatory standards*** (i.e., consent process): no issues.

6.6 ***Timing of the trial***: based on our survey study and the feasibility trial we know that surgeons are willing to enroll most patients to a trial of simultaneous versus staged resection and that there is equipoise in terms of preference. We therefore believe that now is the best time for a trial such as this one to take place.

6.7 ***Standardization of the surgical intervention***: our feasibility trial demonstrated that there are important differences between centres regarding how the operation is performed (technical differences that may lead to different surgical outcomes). Also, there are varied practices on the administration of perioperative chemotherapy between centres (procedural differences that may lead to different long-term oncological outcomes, like disease free survival). We believe that enforcing specific surgical technique (i.e., liver or colon resection first) or administration of chemotherapy would be difficult and would limit recruitment. For that reason, we agree on a more pragmatic approach for this trial, allowing for differences in surgical technique or administration of chemotherapy.

6.8 ***Patient preferences***: our feasibility trial demonstrated that most eligible patients agreed to undergo simultaneous resection of both the liver and the primary tumour at the same time. It is possible that patients have a preference to simultaneous resection as they would avoid a second operation. For those

patients, we will emphasize that at the moment, we do not have a clear understanding of the long-term effects of simultaneous versus staged resections, that there is equipoise in the surgical community, and therefore the need for the trial.

6.9 ***Surgeon preferences***: our survey and feasibility trial showed that surgeons were willing to enroll most patients to a trial of simultaneous resection. There were some patients that although eligible for simultaneous resection, the surgeon did not agree to enroll given the complexity of the operation required. We plan to exclude such patients that require a major liver resection and a complex colorectal resection from a future trial (see Chapter 5, section 2.3.2 Exclusion criteria). It is unclear if surgeons consider patients requiring simple liver and simple colorectal resection good candidates for the larger trial. It is possible that simultaneous resection is already considered standard for these patients, however, this trial is not able to provide that answer, since it did not have a staged approach arm.

6.10 ***Referring physician preferences***: potential participants who are referred to the trial institution for simultaneous resection will lose the relationship established with their local surgeons. Referring physicians are hesitant to refer these patients to the trial institution because of fear of losing that patient-physician relationship. By engaging referring surgeons, for example, by using population-based databases, we will be able to identify potential participants and engage surgeons with the trial, obtaining their consent to approach their

patients and allowing them to discuss with their patients the trial, so that they can feel and become part of the research team. Medical oncologists can also be included in this category as the decision to proceed with chemotherapy around the time of surgery is left to medical oncologist, which could alter trial participation.

6.11 ***Funding***: no issues

7. ACKNOWLEDGMENTS

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8. DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figure and Table Legend

Figure 1. Patient Flow. Patients meeting inclusion criteria: potentially eligible patients. Eligible patients: patients meeting eligibility criteria.

Table 1. Baseline patient characteristics. ECOG: European Cooperative Oncology group. ASA: American Society of Anesthesiologists. CEA: carcinoembryonic antigen.

Table 2. Perioperative characteristics. * Multivisceral resection included: tail pancreas and spleen, duodenum, abdominal wall, ovaries, and diaphragm. pRBC: packed red blood cells.

Table 3. Postoperative outcomes.

Table 4. Challenges and opportunities for improvement in the RESECT trial

Supplement Table 1. Types of major postoperative complications (Clavien-Dindo ≥3)

Figure 1: Patient Flow. Patients meeting inclusion criteria: potentially eligible patients: Eligible patients: patients meeting eligibility criteria.

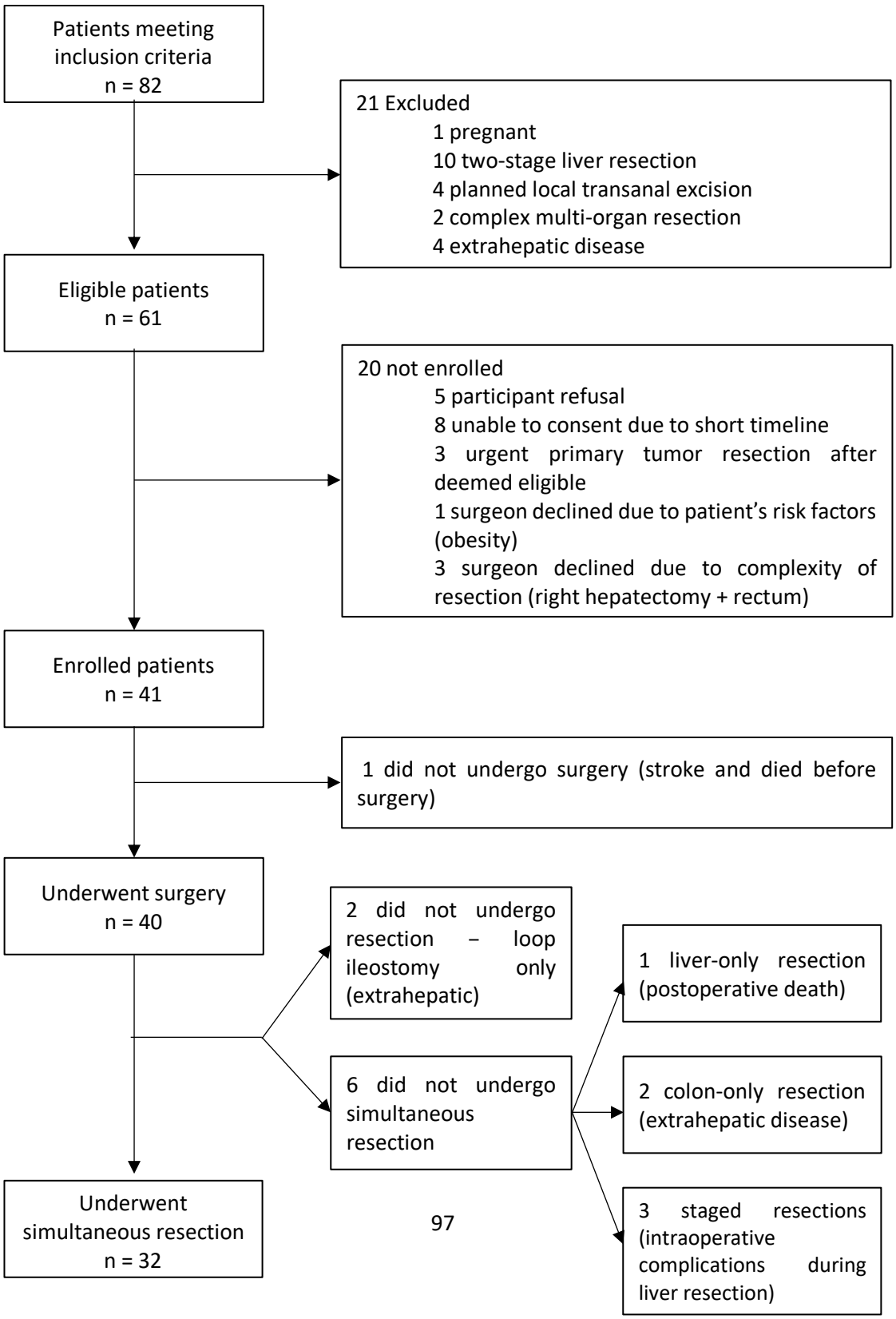

Table 1. Baseline patient characteristics. ECOG: European Cooperative Oncology group. ASA: American Society of Anesthesiologists. CEA: carcinoembryonic antigen

Variable	**n=41**
Age median (IQR)	57 (50 to 67)
Female sex n (%)	13 (32%)
Charlson Comorbidity Index n (%)	
0	3 (7%)
1	7 (17%)
≥ 2	31 (76%)
ECOG Performance Status	
ECOG 0 n (%)	19 (58%)
ECOG 1 n (%)	13 (39%)
ASA Physical Status Classification	
ASA 3 n (%)	15 (38%)
ASA 4 n (%)	25 (63%)
Primary n (%)	
Right and transverse colon	12 (29%)
Left and sigmoid colon	11 (27%)
Rectum	18 (44%)
Number of liver lesions (radiology) (median, IQR)	2 (1 to 3)
Max size liver lesions (radiology) (median, IQR) [mm]	19 (14 to 31)
Bilateral liver lesions (radiology) n (%)	17 (42%)
Preoperative CEA (median, IQR) [ug/L]	4.7 (2.3 to 22)
Presurgical treatment (diversion) n (%)	3 (7.3%)
Neoadjuvant therapy	
chemotherapy n (%)	27 (68%)
number of cycles (median, IQR)	6 (5 to 8)
palliative intent n (%)	9 (22%)
radiation therapy n (%)	16 (39%)

Table 2. Perioperative characteristics. * Multivisceral resection included: tail pancreas and spleen, duodenum, abdominal wall, ovaries, and diaphragm. pRBC: packed red blood cells.

Variable	Patients who underwent simultaneous liver and colon surgery n=32
Operative approach n (%)	
Laparoscopic	13 (41%)
Laparoscopic converted to open	1 (3%)
Open	18 (56%)
Midline incision	18
Subcostal incision	1
Liver as first organ resected n (%)	24 (75%)
Multivisceral resection* n (%)	6 (19%)
Liver resection type n (%)	
Right hemihepatectomy	6 (19%)
Right posterior sectionectomy	5 (16%)
Left hemihepatectomy	3 (9%)
Left lateral sectionectomy	8 (25%)
Wedge resections	10 (31%)
Number of segments resected median (IQR)	2 (2 to 4)
Colon Resection Type n (%)	
Right hemicolectomy	10 (31%)
Left colectomy / sigmoidectomy	2 (6%)
Low anterior resection	14 (44%)
Abdominoperineal resection	5 (13%)
Subtotal colectomy	2 (6%)
Intraoperative blood loss (median, IQR) [mL]	615 395 to 1000)
Liver surgery	400 (300 to 700)
Colon surgery	200 (100 to 375)
Receipt of transfusion of blood products n (%)	8 (25%)
Receipt of transfusion of PRBC n (%)	5 (16%)
Number of pRBC transfused (median, IQR)	2 (1 to 3)
OR Time (median, IQR) [min]	381 (269 to 425)
Liver surgery	181 (95 to 252)
Colon surgery	174 (124 to 226)

Table 3. Postoperative outcomes

Outcomes	**Patients who underwent simultaneous liver and colon surgery n=32**
Length of hospital stay (median, IQR) [days]	10 (6 to17)
Readmission n (%, 95% CI)	6 (19%, 9 to 35%)
90-day all postoperative morbidity (Clavien-Dindo Grade 1 to 5) n (%, 95% CI)	22 (69%, 51 to 82)
90-day major postoperative morbidity (Clavien-Dindo Grade $\geq$3) n (%, 95% CI)	13 (41%, 26 to 58%)
Non-operative re-intervention n (%, 95% CI)	13 (41%, 26 to 58%)
Operative re-intervention n (%, 95% CI)	3 (9%, 3 to 24%)
90-day postoperative mortality n (%, 95% CI)	2 (6%, 1.7% to 20%)
Comprehensive complication index median (Median, IQR)	35 (29 to51)

Table 4. Challenges and opportunities for improvement in the RESECT trial

Variable	Challenge	Opportunity
Study population	Patients with complex disease are not candidates	Exclude patients requiring complex surgery
Study intervention	Recruitment difficulty "Level 2"	Describe the trial as practice changing / innovative
Blinding methods	Not possible to blind patients, outcome assessors or surgeons	Blind statisticians for primary outcome
Statistical considerations	High proportion of enrolled patients not undergoing resection	Adjust sample size based on the findings of the pilot study
Ethical standards	NA	NA
Timing of the trial	Surgeons agree to enroll most patients to trial.	Now is the best time for this trial given equipoise
Standardization	Important centre-based differences on surgical technique	Pragmatic trial design
Patient preference	Patients may wish to undergo only one surgery	Explain importance clinical equipoise
Surgeon preference	Surgeon not willing to randomize complex cases	Exclude these patients from the larger trial
Referring physician preference	Surgeons not willing to refer to trial institution	Involve surgeons in trial procedures
Funding	NA	NA

Supplementary Tables

Supplement Table 1: Types of major postoperative complications (Clavien-Dindo ≥3)

Event	Patients who underwent simultaneous liver and colon surgery n=32
Intra-abdominal abscess	7
Colorectal anastomotic leak	4
Pneumonia	2
Septic shock	3
Hemorrhage	1
Bile leak (liver surface)	1
Post hepatectomy liver failure	1
Wound dehiscence	2
Liver related n (%)	8 (25%)
Colorectal related	5 (16%)

9. REFERENCES

1. Committee CCSA. Canadian Cancer Statistics 2019. *Canadian Cancer Society.* 2019.
2. Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev.* 2015;41(9):729-741.
3. Bogach J, Wang J, Griffiths C, et al. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cohort study. *Int J Surg.* 2020;74:68-75.
4. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(7):874-901.
5. Engstrom PF, Arnoletti JP, Benson AB, 3rd, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. *J Natl Compr Canc Netw.* 2009;7(8):778-831.
6. Serrano PE, Gu CS, Husien M, et al. Risk factors for survival following recurrence after first liver resection for colorectal cancer liver metastases. *Journal of surgical oncology.* 2019; 120(8):1420-1426.
7. Kim HS, Lee JM, Kim HS, et al. Prognosis of Synchronous Colorectal Liver Metastases After Simultaneous Curative-Intent Surgery According to Primary Tumor Location and KRAS Mutational Status. *Ann Surg Oncol.* 2020;27(13):5150-5158.
8. Boudjema K, Locher C, Sabbagh C, et al. Simultaneous Versus Delayed Resection for Initially Resectable Synchronous Colorectal Cancer Liver Metastases: A Prospective, Open-label, Randomized, Controlled Trial. *Ann Surg.* 2021;273(1):49-56.
9. Vallance AE, van der Meulen J, Kuryba A, et al. The timing of liver resection in patients with colorectal cancer and synchronous liver metastases: a population-based study of current practice and survival. *Colorectal Dis.* 2018;20(6):486-495.
10. Abelson JS, Michelassi F, Sun T, et al. Simultaneous Resection for Synchronous Colorectal Liver Metastasis: the New Standard of Care? *J Gastrointest Surg.* 2017;21(6):975-982.
11. Idrees JJ, Bagante F, Gani F, et al. Population level outcomes and costs of single stage colon and liver resection versus conventional two-stage approach for the resection of metastatic colorectal cancer. *HPB (Oxford).* 2019;21(4):456-464.
12. Serrano PE, Gafni A, Parpia S, et al. Simultaneous resection of colorectal cancer with synchronous liver metastases (RESECT), a pilot study. *Int J Surg Protoc.* 2018;8:1-6.
13. Bismuth H. Revisiting liver anatomy and terminology of hepatectomies. *Ann Surg.* 2013;257(3):383-386.
14. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg.* 2005;12(5):351-355.

15. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol.* 2007;14(12):3481-3491.
16. Chen H, Merchant NB, Didolkar MS. Hepatic resection using intermittent vascular inflow occlusion and low central venous pressure anesthesia improves morbidity and mortality. *J Gastrointest Surg.* 2000;4(2):162-167.
17. Hughes MJ, Ventham NT, Harrison EM, Wigmore SJ. Central venous pressure and liver resection: a systematic review and meta-analysis. *HPB (Oxford).* 2015;17(10):863-871.
18. Wright JR, Bouma S, Dayes I, et al. The importance of reporting patient recruitment details in phase III trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(6):843-845.
19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery.* 2004;240(2):205.
20. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg.* 2013;258(1):1-7.
21. Chua HK, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. *Dis Colon Rectum.* 2004;47(8):1310-1316.
22. Serrano PE, Gafni A, Gu CS, et al. Positron Emission Tomography-Computed Tomography (PET-CT) Versus No PET-CT in the Management of Potentially Resectable Colorectal Cancer Liver Metastases: Cost Implications of a Randomized Controlled Trial. *J Oncol Pract.* 2016;12(7):e765-774.
23. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.
24. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol.* 1997;50(4):441-450.
25. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(1):139-144.
26. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer.* 2007;110(1):196-202.
27. Ercolani G, Grazi GL, Ravaioli M, et al. Liver resection for multiple colorectal metastases: influence of parenchymal involvement and total tumor volume, vs number or location, on long-term survival. *Arch Surg.* 2002;137(10):1187-1192.
28. Capussotti L, Ferrero A, Vigano L, Ribero D, Lo Tesoriere R, Polastri R. Major liver resections synchronous with colorectal surgery. *Ann Surg Oncol.* 2007;14(1):195-201.

29. Wei AC MC, Coburn N, Cleary SP, Law C, Greig PD, et al. A Phase II multicenter study of metastasectomy of intra- and extra-hepatic metastases from colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(supple 4):abstr 482.
30. Griffiths C, Bogach J, Simunovic M, et al. Simultaneous resection of colorectal cancer with synchronous liver metastases; a practice survey. *HPB : the official journal of the International Hepato Pancreato Biliary Association.* 2020;22(5):728-734.
31. Biffl WL, Spain DA, Reitsma AM, et al. Responsible development and application of surgical innovations: a position statement of the Society of University Surgeons. *J Am Coll Surg.* 2008;206(6):1204-1209.
32. Cook JA, Ramsay CR, Norrie J. Recruitment to publicly funded trials--are surgical trials really different? *Contemp Clin Trials.* 2008;29(5):631-634.

Chapter 4.

Use of population-based electronic databases for the identification of patients with synchronous colorectal cancer and liver metastases potentially eligible for a surgical trial.

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Introduction to Chapter 4.

This chapter does not describe a type of surgical trial, but a study designed to increase the number of potential participants eligible for the RESECT trial presented in Chapter 3, a potential solution to recruitment issues. Although a large effort was undertaken to incentivize surgeons to refer patients diagnosed with synchronous colorectal cancer liver metastases to the trial institution prior to resection of the primary tumour (patient population of the RESECT trial), we realized that we would only accrue a small percentage of eligible patients.

With the main goal of determining the value of population-based databases to identify potential trial participants diagnosed with colorectal cancer and liver metastases, we developed the study presented in this chapter that was performed alongside the RESECT trial. This is a prospective cohort study evaluating the use of electronic databases to identify all patients in the LHIN-4 region eligible for the RESECT trial at the Juravinski Hospital. By identifying all eligible patients, we could determine the percentage of patients that were not being referred for the RESECT trial prior to surgery, and therefore not enrolled. The population-based datasets used in this study are available in the LHIN-4 region of the province of Ontario, Canada. They are also available with different names but similar uses in the other regions of the province.

We planned to include this method of identifying potential participants in the design of a larger trial (i.e., RESECT-RCT), presented in Chapter 5.

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Running head: Electronic databases increase trial accrual

Synopsis for Table of Contents:

- Traditional methods of patient accrual for cancer surgical trials are low yielding. Electronic databases have the potential to improve accrual.
- Proportion of patients identified using population-based databases versus traditional accrual methods to surgical trial: "Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases (RESECT)" was compared.
- Population-based methods of trial accrual are able to identify potentially eligible participants for the RESECT trial, though optimal accrual likely requires the use of traditional methods as well.

ABSTRACT

Background

Number of patients identified using population-based databases versus traditional accrual methods to surgical trial: "Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases (RESECT)" was compared.

Methods

Electronic database (e-PATH) was interrogated for colorectal cancer patients biweekly. Radiological images database (OneView) identified those with liver metastases (Level-1-screening). Reports were interrogated to identify potentially eligible patients for RESECT (Level-2-screening). Hepatobiliary surgeon reviewed radiology images to identify eligible patients for RESECT (Level-3-screening). We evaluated the use of the population-based electronic databases to identify patients that could be potentially accrued to the RESECT trial and compared it to the traditional methods used to accrue patients for that same trial during the same time-period.

Results

Population-based methods identified 90/803 (11%) colorectal cancer liver metastases patients (Level-1-screening). Level-2-screening identified 60/90 (67%) potentially eligible patients for RESECT (OneView radiological reports). Of these, 18/90 (20%) were eligible following radiographic images review (Level-3-screening). Traditional methods identified 38 patients with liver metastases and Level 2 screening yielded 27/38 (71%) potentially eligible patients, and 14/38 (37%) eligible patients (Level-3-screening). There were 26 patients identified by both methods. There were 12 patients identified by population-based

methods alone and 8 patients by traditional methods alone. Six eligible patients were identified by both methods. Baseline characteristics were similar between groups.

Conclusions

Population-based methods of trial accrual are able to identify potentially eligible participants for the RESECT trial, though optimal accrual likely requires the use of traditional methods as well.

Keywords:

Accrual, clinical trial, colorectal cancer, metastases, databases

BACKGROUND

Approximately half of surgical clinical trials fail to reach their target sample size [1]. Low rate of recruitment is a major barrier to the completion of clinical trials. Due to a variety of reasons, this recruitment issue is more evident in surgical trials for patients with cancer (i.e., patients are in a rush to be treated, leaving little time to explore clinical trials) [2]. While 70% of patients report an inclination to participate in clinical trials, less than 5% of patients being treated at cancer centres across North America are enrolled in a clinical trial each year [3,4]. Poor accrual is the main factor associated with early trial termination in up to 30% of clinical trials in cancer [5-7]. Traditional accrual to cancer surgery trials requires involved clinicians (e.g., surgeons) receiving a patient referral, to recognize that a specific patient is trial-eligible, and then approaching the patient for enrollment.

Alternate methods to recruit patients to clinical trials in cancer could decrease early trial termination, expediting trial completion [8,9]. Some population-based recruitment methods, such as registries and databases, have been used in the past to increase enrolment to clinical trials by identifying eligible participants based on baseline characteristics [10,11]. These methods are attractive due to the availability of a large pool of potentially eligible candidates, especially for multicentre studies, or those involving patients with rare diseases. These methods, however, have not been tested in surgical trials, in which accrual occurs prior to surgery, and therefore there is a rush to identify patients within a limited amount of time, an issue that is even more relevant for patients with a diagnosis of cancer.

Surgery for patients with synchronous colorectal cancer and liver metastases can be performed via the traditional staged resection approach, where patients usually undergo

primary tumour resection followed weeks later by a liver resection or via the more recently used and not fully researched, simultaneous resection, involving a single operation to resect both sites (i.e., primary colorectal cancer and liver metastases) [12,13]. Our group designed a multi-institutional single arm surgical trial called the "Simultaneous Resection of Colorectal Cancer with Synchronous Liver Metastases" (RESECT) trial to evaluate feasibility of a larger randomized trial evaluating efficacy of simultaneous resection.

Local Health Integration Network (LHIN) 4 region (population 1.4 million) is one of fourteen health administrative regions in the province of Ontario [14]. All hospital and clinic pathology reports related to cancer from each health administrative region across Ontario are collected and codified in real-time (i.e., as soon as the report is available on the patient's institution's medical record) to the e-PATH electronic database at Cancer Care Ontario (the agency overseeing the quality of cancer services in Ontario). OneView is an electronic repository of radiology reports and imaging (e.g., computed tomography (CT) and magnetic resonance imaging (MRI) scans) done at each LHIN4 hospital. As mentioned, in most jurisdictions traditional methods of patient accrual to surgical cancer clinical trials usually results in low accrual rates, resulting in early trial termination. We evaluated the use of the population-based electronic databases to identify patients that could be potentially accrued to the RESECT trial and compared it to the traditional methods used to accrue patients for that same trial during the same time-period [15].

MATERIALS AND METHODS

Study Design and Setting

The LHIN 4 region contains a population of 1.4 million and 11 hospitals along with approximately 50 surgeons that provide surgical care to patients with colorectal cancer [16]. All major liver surgery is performed at a single teaching site by one of five hepatobiliary surgeons. The RESECT trial was a multi-institutional, single-arm clinical trial that recruited patients from February 1, 2017, to November 30, 2019, in the province of Ontario. It aimed to determine the feasibility of performing a trial of simultaneous resection of the liver and primary tumour among patients who present with resectable synchronous colorectal cancer liver metastases. The RESECT trial included three sites where surgery could be performed. Two sites outside the LHIN 4 region and one site within the LHIN 4 (Juravinski Hospital). The Juravinski Hospital is the only hospital, within the LHIN 4 region, where all major liver resections occur. Our current study evaluated two methods to identify LHIN 4 patients eligible for the RESECT trial over the truncated interval of February 1, 2017, to March 30, 2019. The institutional research ethics board approved this study.

Study Population and Groups

A research assistant prospectively reviewed the electronic pathology database (e-PATH) biweekly to identify patients diagnosed with colorectal cancer by endoscopic or percutaneous biopsy (approximately 20 new patients every 2 weeks). Eligible histologies included adenocarcinoma, including signet ring cell carcinoma, adenosquamous carcinoma, carcinosarcomas, and mixed adenocarcinoma-neuroendocrine tumour (adenocarcinoma with neuroendocrine differentiation). Imaging reports on OneView were screened by that same research assistant to identify patients with liver metastases (Level 1 screening). This process took no more than 1 hour every two weeks. One research assistant

then performed Level 2 screening on those patients identified in Level 1 (approximately 5 patients every two weeks), by identifying potentially eligible patients to the RESECT trial. This consisted of excluding pregnant patients, patients with extrahepatic metastatic disease (other than lung), patients that had their primary tumour already resected (either before the biopsy was obtained or after initial imaging due to bleeding or obstruction). Patients that were excluded were reviewed by a second research assistant to confirm they indeed met the exclusion criteria. A correlation Kappa value was not calculated for this level as the second research assistant only reviewed those patients that were excluded. Agreement at this level was obtained by consensus. Level 2 screening took no more than 30 minutes every 2 weeks. Level 3 screening consisted of a hepatobiliary surgeon reviewing OneView images in detail to identify eligible patients for RESECT trial (two patients per month). This level included the exclusion of patients in which the assessment of the imaging indicated unresectable disease in the liver, the need for resection of more than one additional pelvic (other than rectum) or abdominal organ (other than liver), or if they had more than three metastatic deposits in the lung. Patients requiring a two-stage liver resection (due to insufficient future liver remnant) were also excluded at this stage. The determination of resectability was a "conservative measure", only patients with clearly resectable disease were considered eligible for the RESECT trial. Those patients that would require neoadjuvant chemotherapy for down-sizing or that would require a two-stage liver resection due to insufficient liver remnant were not considered eligible. Level 3 screening happened within 4 weeks of the first identification of each patient on e-PATH to allow for time to pass between the first biopsy and the first CT scan.

Traditional methods of patient accrual involved identifying the population of patients with colon cancer and liver metastases by screening all new patients referred to the surgical clinics at the Juravinski Hospital (5 hepatobiliary surgeons and 4 colorectal surgeons) and selecting those with a new diagnosis of colorectal cancer. Imaging reports of selected patients with a diagnosis of colorectal cancer were further reviewed to identify those with liver metastases (Level 1 screening). A research assistant then identified potentially eligible patients for the RESECT trial by reviewing the inclusion and exclusion criteria of the trial (Level 2 screening). Potentially eligible patients were then reviewed by a hepatobiliary surgeon (Level 3 screening) to confirm eligible patients for the trial, which included a detailed review of the surgical aspects of the case (i.e., need for two-stage liver resection, need for additional organ resection, presence of more than three metastatic deposits in the lung, etc.). The RESECT trial was advertised to surgeons, medical oncologists, and radiation oncologists at weekly Cancer Centre multidisciplinary rounds, by hanging posters in surgeons' and oncologists' clinics, at national or regional surgical rounds, and via letters, emails, and faxes to community surgeons, medical oncologists and radiation oncologists that explained the study and asked for prompt referral to the Regional Cancer Centre when a potential patient was identified. Patients were accrued to the RESECT trial using traditional methods only.

Data collection and variables

Variables collected from e-PATH included patient demographics: age, sex, and institution where the biopsy took place. Other variables included: histology, and location of the primary colorectal tumour. Variables collected from One View included: type of imaging

performed (CT or MRI), location within the liver (laterality), number and size of liver metastases, type of resection required for the liver (minor or major liver resection) [17], type of colorectal resection required (i.e., need for additional organ resection other than the location of the primary tumour), presence of lung metastases (≤3 deposits) and presence of extrahepatic metastases other than lung. The same variables were collected for patients identified using traditional methods, however they were extracted from the hospital's medical record system.

Outcomes and Analysis

The primary outcome of this study was patient being eligible for the ongoing RESECT trial.[18] The proportion of patients identified by each group (traditional versus population-based methods) was calculated by dividing the number of patients identified by one group alone by the total number of patients identified by both groups alone without overlap. The population-identification ratio for eligible patients was calculated by dividing "the number of patients prospectively identified using electronic databases alone" by "the number of patients identified through traditional methods alone".

Patient demographics were reported as proportions and absolute counts, or median and range when appropriate. For eligible patients, a population-identification ratio of ≥1.3 was considered to be clinically significant prior to the initiation of the study (arbitrary measurement). All analyses were conducted using R (R Foundation for Statistical Computing, version 3.5.0, Vienna, Austria) [19].

RESULTS

Population-based accrual methods

The e-PATH search revealed 803 patients diagnosed with colorectal cancer from February 2017 to March 2019, with 90/803 (11%) patients having a primary colorectal cancer with imaging on OneView suggestive of liver metastases (Level 1 screening). Body imaging was performed at a median of 15 days (range: 5 to 37) from the biopsy date. Of those 90 patients identified with liver metastases on imaging, 60/90 (67%) were classified as potentially eligible for the RESECT trial by reading OneView radiological reports on Level 2 screening (Figure 1), by excluding pregnant patients, patients with extrahepatic metastatic disease (other than lung), patients that had their primary tumour already resected (either before the imaging was obtained or after initial imaging due to bleeding or obstruction). Upon Level 3 screening, performed by a hepatobiliary surgeon, 42 patients were excluded, leaving 18/90 (20%) patients eligible for the RESECT trial through the population-based electronic database accrual method. In Level 3 screening, most patients were excluded due to the presence of more than three metastatic deposits in the lung (n=16), followed by unresectable hepatic lesions (n=10) (Table 1). Of these 18 eligible patients, there were 4 patients who were eventually found to have undergone colorectal resection after 2 weeks of being categorized as eligible by the hepatobiliary surgeon when the pathology report of their colorectal tumour was found in later reports of the e-PATH database.

Traditional accrual method

There were 38 patients identified with colon cancer and liver metastases via traditional patient accrual methods. Level 2 screening yielded 27/38 (71%) potentially eligible patients for the RESECT trial based on review of clinical notes and imaging reports of patients attending the Juravinski Hospital surgical clinics. Nine of these 27 patients were also found

via population-based electronic database methods. Level 3 screening, including a detailed review of the surgical aspects of the case by a hepatobiliary surgeon (i.e., need for two-stage liver resection, need for additional organ resection, presence of more than three metastatic deposits in the lung, etc.) identified 14/38 (37%) eligible patients for RESECT (Figure 1). The most common reason for exclusion was the finding that the liver lesions were benign and not metastases (n=4), followed by unresectable liver lesions (n=2) and need for two-stage liver resection (n=1) (Table 1). Of these 14 patients, 6 were also found via population-based electronic database methods. The reasons that the other 8 patients were only found via traditional methods only and not via population-based methods were: biopsy not reported by e-PATH therefore missed (n=1), biopsy showed high grade dysplasia and not invasive carcinoma, therefore not reported to e-PATH (n=2), patients diagnosed outside of the LHIN-4 catchment area (n=2) and patients had undergone biopsy of the colorectal tumour prior to the initiation of this study (n=3) (Figure 1).

Baseline characteristics of eligible patients

Patients identified via population-based or traditional methods were similar in age (median 64 vs. 57), however, patients identified via population-based methods alone (excluding patients identified by both methods) were more likely to be older compared to patients identified via traditional methods alone (median 69 vs. 49 years old, respectively). They were also more likely to have had a biopsy further away from the hepatobiliary cancer centre (median 20 vs. 0 Km away, respectively, the location of the primary tumour, number and size of liver metastases, the extent of liver disease (one lobe versus both lobes of the liver), and the need for major liver resection were similar between groups (Table 2). A few

patients were identified as requiring resection of additional abdominal or pelvic organ other than the primary tumour (3/26 patients, 12%), and those additional organs included: spleen, pancreas, and abdominal wall.

Population identification ratio

After Level 3 screening, there were 26 eligible patients identified by both methods, with 20 eligible patients identified without overlap (Table 3). There were 6 eligible patients that were identified by both methods. The population-identification ratio for eligible patients was 1.5 (12/8) (Table 3). Of the 14 eligible patients identified by traditional methods (8 by traditional methods alone and 6 by both methods), 10/14 (71%) were enrolled in the study. The other four patients were not enrolled due to: patient declined to participate (n=1), surgeon's preference (n=2), and progression of metastatic disease (n=1). Of the 18 eligible patients identified by population-based methods, 6 were found by traditional methods also and were enrolled in the study. The other 12 patients were not approached to participate in the study and were not referred to the hepatobiliary cancer centre before they underwent colorectal resection.

DISCUSSION

In this study, the use of population-based methods was able to identify almost three times as many potentially eligible patients, and 50% more eligible patients for the RESECT trial compared to traditional methods of enrolment. Eligible patients identified via both methods had similar baseline characteristics with the exception that patients identified via population-based methods were being treated at a region further away from the hepatobiliary cancer centre. Considering that 70% of eligible patients identified via

traditional methods were eventually enrolled in the RESECT study, it is possible that using population-based accrual methods, the number of patients enrolled could have been much greater. Population-based cancer registries are not commonly used to identify patients eligible for surgical trials. Surgical resection for most cancers should happen relatively soon after diagnosis and confirmation of resectability; therefore, population-based methods to screen and approach patients should have the capability of identifying eligible patients in a timely manner (i.e., within a few weeks of diagnosis). The short time window between biopsy and imaging means that our research team would have been able to contact the treating surgeon within a reasonable amount of time prior to consideration of surgical resection of the primary tumour. It is important to remember that these patients are not always upfront resectable, instead, sometimes, they require neoadjuvant treatments. Our group has designed the protocol for a randomized trial (RESECT-RCT) and given the success of the findings of this study, we plan to trial the use of population-based methods to increase accrual.

There are few studies that aim to increase accrual to surgical clinical trials for patients with colorectal cancer. A systematic review by Tan et al, showed that cancer registries are the most frequent population-based databases used to recruit potential participants to clinical trials (of the 25 citations found, 14 were from cancer registries). However, of those, only one study included patients with colorectal cancer, and that study was aimed to recruit family members of probands with colorectal cancer for screening [20].

The proportion of potentially eligible patients who were found to be eligible for the RESECT trial after review by a surgeon was lower in the population-based group compared

to the traditional methods group (20% vs. 37%). Most patients became ineligible due to the presence of extrahepatic disease not previously mentioned in the radiology report (i.e., more than three sites of metastatic deposits in the lungs) or unresectable liver disease. It is possible that a research coordinator can be taught to identify those patients, which would lead to a more streamlined use of resources. It is also conceivable that machine learning could be used to identify potentially eligible patients for the trial based on the radiological report description (i.e., mention of liver metastases).

There are some limitations to our current study. The small number of patients who are eligible for the RESECT trial makes comparisons between groups difficult, and therefore the applicability of population-based methods to different clinical trials with broader patient eligibility is unknown. In addition, this study aimed to only test the feasibility of e-PATH and One View to identify potential participants for a clinical trial; we did not attempt to contact treating physicians (directly involved with patients' circle of care) to approach patients to participate in the study. Therefore, we do not know if the proportion of patients enrolled using population-based methods would be the same as that of traditional methods. It could be that tumour characteristics (i.e., rectal primary), surgeons' or patients' preferences or even geographical location (i.e., distance from the hepatobiliary cancer centre) are significant barriers for patient enrollment, making the true delta between both methods smaller than what we found with this study [21]. Also, a significant number of eligible patients (4/18, 22%) identified via population-based methods, underwent colorectal resection within two weeks of being determined eligible for the study, leaving a small window to potentially attract them to the RESECT trial. It is also not known if this method

of identifying patients for a clinical trial would be useful in other jurisdictions as the databases mentioned are unique to Ontario, Canada.

CONCLUSIONS

The use of electronic networks to identify patients eligible for ongoing surgical cancer trials represents a novel technique for improving enrolment to these types of surgical trials. These electronic registries are updated prospectively in "real-time", and as such, they are feasible to use for enrolment purposes, requiring few additional resources from the research team as the database is already being used for other reasons. This approach also avoids relying exclusively on regional surgeons, oncologists, or gastroenterologists to refer patients for clinical trial purposes, which is known to be an ineffective way to accrue patients (i.e., rate of enrolment of only 10-20% of eligible patients) [22,23]. With adequate training, population-based methods seem to yield a very similar patient population to that of traditional methods, it is easily accessible utilizing existing resources; therefore, it can keep the cost of accrual down and the effort of the research staff to accrue patients low. However, these methods may miss patients that would otherwise be captured by traditional methods (i.e., biopsy showing high grade dysplasia, patients with biopsies performed outside the catchment area or patients that require downsizing neoadjuvant chemotherapy or portal vein embolization), therefore, both methods of accrual are necessary for optimal recruitment.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Table 1. Reasons for exclusion for potential participants identified via population-based and traditional methods of accrual. Extrahepatic disease (extrahepatic metastases other than <4 sites in the lung), Local excision (primary tumour treated with local trans-anal excision).

Reasons for Exclusion	**Population-Based Methods Alone (n= 51)**	**Both Methods (n= 9)**	**Traditional Methods Alone (n= 18)**
Unresectable	10	1	2
Benign Liver Lesions	1	-	4
Extrahepatic Disease	16	-	-
Not Fit for Surgery	3	-	-
Urgent Colon Resection	9	-	1
Prior Liver Resection	-	1	1
2-Stage Liver Resection	-	-	1
Local Excision	-	-	1
Pregnancy	-	1	-

Table 2. Baseline characteristics of eligible patients. Distance refers to distance from the hepatobiliary cancer centre to where the colorectal biopsy was taken. CT: computed tomography, MRI: magnetic resonance imaging. Bilateral refers to bilobar liver metastases. Additional organ refers to additional abdominal organs involved with the primary colorectal cancer. *There were 6 patients identified by both methods.

Variable	Population-Based Methods Alone n= 18	Traditional Methods Alone n= 14	Total n= 26*
Age, median (range)	64 (35 to 91)	57 (35 to 76)	61 (35 to 91)
Female Sex, n (%)	9 (50%)	4 (29%)	10 (39%)
Distance (Km) median (range)	20 (0 to 53)	0 (0 to 53)	3.4 (0 to 53)
Primary tumour, n (%)			
right sided	5 (28%)	4 (29%)	9 (35%)
left sided	9 (50%)	4 (29%)	10 (39%)
rectum	4 (22%)	6 (43%)	7 (27%)
CT	9 (50%)	4 (29%)	11 (42%)
MRI	2 (11%)	3 (21%)	3 (12%)
CT and MRI	7 (39%)	7 (50%)	12 (46%)
Number of liver metastases, median (range)	2 (1 to 8)	2.5 (1 to 9)	2 (1 to 9)
Bilateral n (%)	10 (56%)	7 (50%)	12 (46%)
Major liver resection, n (%)	11 (61%)	10 (71%)	18 (69%)
Additional organ, n (%)	3 (17%)	2 (14%)	3 (12%)
Size metastases, median (range)	23 (6 to 70)	36 (7 to 82)	26 (6 to 82)

Table 3. Population-identification ratio based on potentially eligible and eligible patients for the RESECT trial. Data presented as count and percentage of the total number of patients found by each method alone, excluding those patients found by both methods. Ratio calculated by dividing the number of patients identified by population-based methods alone by the number of patients identified by traditional methods alone.

Level of screening	Population-based methods	Both methods	Traditional methods	Total (each method alone)	Population Identification Ratio
Level 1 screening (population size)	803	-	-	-	-
Level 2 screening (potentially eligible)	51	9	18	69	2.8
Level 3 screening (eligible)	12	6	8	20	1.5
Enrolled patients	-	6	4	-	-

Figure 1. The Population-based electronic database method versus traditional methods of identifying and screening eligible patients for the RESECT trial.

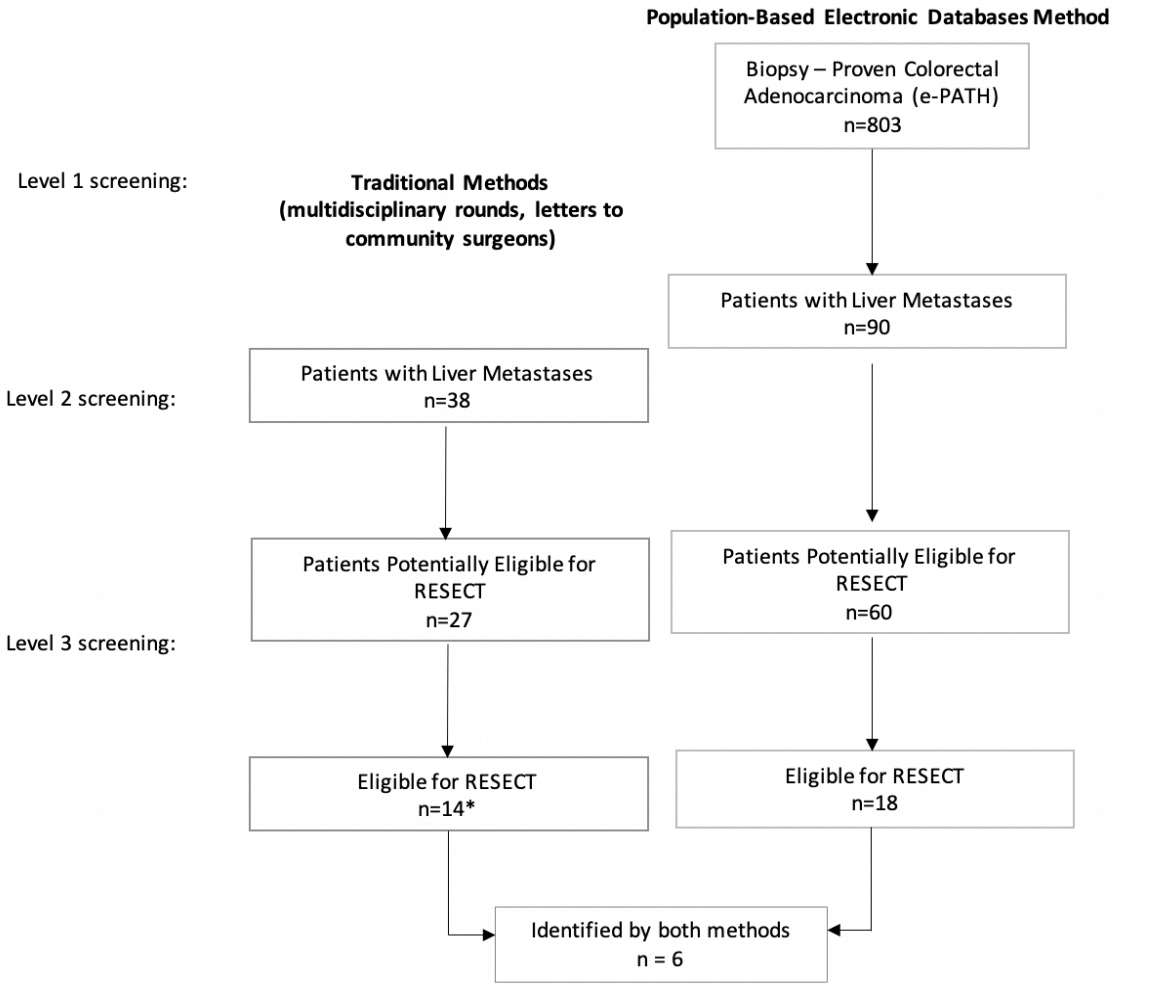

Figure legend: Level 1: RA obtains e-PATH file and identifies sample population using OneView reports. Level 2: RA identifies potentially eligible patients for RESECT by reading OneView reports. Level 3: Surgeon identifies eligible cases by detailed review of OneView and available clinical notes). Level 3: Surgeon identifies eligible cases by detailed review of OneView and available clinical notes). *There were 8 patients not found by the population-based methods: 1 patient missed, 2 patients were out of LHIN-4, 2 patients had biopsies that were negative for colorectal cancer, 3 patients had biopsies outside of the time-period of the study. RA: research assistant.

REFERENCES

1. McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials.* 2006;7:9.
2. Rosenthal R, Kasenda B, Dell-Kuster S, et al. Completion and Publication Rates of Randomized Controlled Trials in Surgery: An Empirical Study. *Ann Surg.* 2015;262(1):68-73.
3. Comis RL, Miller JD, Aldigé CR, Krebs L, Stoval E. Public attitudes toward participation in cancer clinical trials. *J Clin Oncol.* 2003;21(5):830-835.
4. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA.* 2004;291(22):2720-2726.
5. Kitterman DR, Cheng SK, Dilts DM, Orwoll ES. The prevalence and economic impact of low-enrolling clinical studies at an academic medical center. *Acad Med.* 2011;86(11):1360-1366.
6. Schroen AT, Petroni GR, Wang H, et al. Achieving sufficient accrual to address the primary endpoint in phase III clinical trials from U.S. Cooperative Oncology Groups. *Clin Cancer Res.* 2012;18(1):256-262.
7. Unger JM, Barlow WE, Ramsey SD, LeBlanc M, Blanke CD, Hershman DL. The Scientific Impact of Positive and Negative Phase 3 Cancer Clinical Trials. *JAMA Oncol.* 2016;2(7):875-881.
8. Unger JM, Cook E, Tai E, Bleyer A. Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. *Am Soc Clin Oncol Educ Book.* 2016;35:185-198.
9. Dilts DM, Cheng SK. The Importance of Doing Trials Right While Doing The Right Trials. *Clin Cancer Res.* 2012;18(1):3-5.
10. Tan MH, Thomas M, MacEachern MP. Using registries to recruit subjects for clinical trials. *Contemp Clin Trials.* 2015;41:31-38.
11. Andersen MR, Schroeder T, Gaul M, Moinpour C, Urban N. Using a population-based cancer registry for recruitment of newly diagnosed patients with ovarian cancer. *Am J Clin Oncol.* 2005;28(1):17-20.
12. Mayo SC, Pulitano C, Marques H, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. *J Am Coll Surg.* 2013;216(4):707-716; discussion 716-718.
13. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* 2016;27(8):1386-1422.
14. Ontario CC. Cancer Care Ontario's Data Book 2014-2015: Section IV: Cancer Pathology Data (ePath). 2015; https://www.cancercare.on.ca/ext/databook/db1415/databook.htm Accessed June 20, 2017.
15. Bogach J WJ, Parpia S, Simunovic M, Hallet J, Serrano PE. Simultaneous versus staged resection for synchronous colorectal cancer liver metastases: A population-based cohort study. *J Clin Oncol.* 2019;37(suppl 4):665.

16. Anderson WG, Flint LA, Horton JR, Johnson K, Mourad M, Sharpe BA. Update in hospital palliative care. *Journal of Hospital Medicine.* 2013;8(12):715-720.
17. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. *Ann Surg.* 2013;257(3):377-382.
18. Serrano PE, Parpia S, Karanicolas P, et al. Simultaneous resection for synchronous colorectal cancer liver metastases: A feasibility clinical trial. *J Surg Oncol.* 2022;125(4):671-677.
19. Kanda Y. [Statistical analysis using freely-available "EZR (Easy R)" software]. *Rinsho Ketsueki.* 2015;56(10):2258-2266.
20. Tan MH, Thomas M, MacEachern MP. Using registries to recruit subjects for clinical trials. *Contemp Clin Trials.* 2015;41:31-38.
21. Griffiths C, Bogach J, Simunovic M, et al. Simultaneous resection of colorectal cancer with synchronous liver metastases; a practice survey. *HPB : the official journal of the International Hepato Pancreato Biliary Association.* 2020;22(5):728-734.
22. Albrecht TL, Eggly SS, Gleason MEJ, et al. Influence of clinical communication on patients' decision making on participation in clinical trials. *J Clin Oncol.* 2008;26(16):2666-2673.
23. Comis RL, Miller JD, Colaizzi DD, Kimmel LG. Physician-related factors involved in patient decisions to enroll onto cancer clinical trials. *J Oncol Pract.* 2009;5(2):50-56.

Chapter 5.

Simultaneous versus Staged Resection of Colorectal Cancer with Synchronous Liver Metastases (RESECT), A Randomized Controlled Trial Protocol

This paper has been submitted for publication in a peer-reviewed journal but not yet published. Once published we will obtain permission to print from the publisher.

Introduction to Chapter 5.

The conduct of the studies included in this thesis gave us the necessary background for the design of a randomized controlled trial (RESECT-RCT), a trial that compares two different types of surgical interventions.

The three different studies included in this thesis (Chapter 2, 3 and 4) gave important lessons and opportunities for improvement that were carefully incorporated in the design of RESECT-RCT. Chapter 2 demonstrated the difficulties of randomizing weeks in advance of a potential participant's operation (i.e., four weeks). We suggested to identify and meet potential participants early in their surgical journey, regardless of whether they end up going to surgery. Surgeons, for the most part, know if a patient that was referred to them with the diagnosis of cancer is a potential candidate for surgery. Most patients are referred with pathological diagnosis or with body imaging (i.e., CT scans or MRI) suggestive of cancer. By discussing with surgeons prior to patient's first clinic visit, we can determine if a patient is likely to undergo surgery soon. If they are, then the research team should be able to explain to patients the potential trials available to them. The research team is also responsible for communicating with the surgeons the trials that are available for their patients. This is important, as for RESECT-RCT a complex coordination process must happen in order to schedule the colorectal and the liver resection the same day. Therefore, the surgeon needs many weeks of preoperative planning prior to surgery.

The pilot study presented in Chapter 3 served to identify the optimal patient population for RESECT-RCT. As previously noted, patients requiring complex colorectal resections and major liver resections (i.e., more than 2 segments) in the same setting would

not be eligible for the trial, as surgeons do not feel comfortable performing a simultaneous operation on these patients. Similarly, patients requiring resection of more than 5 liver segments or that have an estimated future liver remnant <30% are not considered good candidates for this trial. The calculation of the sample size was also derived from lessons learned from this feasibility study, by adding 20% more participants to each arm to account for those participants randomized to the simultaneous approach that will not undergo simultaneous resection.

For participants to be eligible for the RESECT-RCT trial, they must be referred to the trial institution prior to surgical resection of the primary tumour, which is sometimes not possible, as we learned with the ACCESS study (Chapter 4), 50% of patients eligible for the trial were not referred prior to surgical resection of the primary tumour and were not included in the RESECT pilot trial. RESECT-RCT will use the electronic population-based datasets explored in Chapter 4, as a separate tool to increase accrual. These tools were investigated in the LHIN-4 region of Ontario, however, given that there are similar entities across Canada, we expect that each centre will be able to use this type of population-based accrual methods. This will be a nested study within RESECT-RCT, as the study presented in Chapter 4 did not approach patients or attempted to enroll them in the trial.

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This protocol has been created in accordance with the requirements for publication by the International Journal of Surgery Protocols.

ABSTRACT

Colorectal cancer liver metastases are considered to be synchronous when the primary tumour is diagnosed at the same time as the liver metastases. Synchronous liver metastases can be resected simultaneously with the primary tumour or as a second staged operation. Simultaneous resection is an attractive option as it decreases the number of operations a patient will have and avoids progression of disease, which can render a patient incurable. However, it could be associated with higher complications including mortality. Observational data suggest similar postoperative complications between simultaneous and staged resections, with a shorter length of hospital stay and costs with the simultaneous approach. A single arm feasibility trial of simultaneous resection and a small, randomized trial of simultaneous versus staged resection showed that of all enrolled patients, 80% undergo simultaneous resection and that postoperative complications are high (40%) but associated with low mortality rate (5%). This randomized trial also suggested that overall survival might be worse for patients undergoing staged resection due to disease progression in between surgeries, leading to unresectable disease. Our feasibility trial of simultaneous resection concluded that although enrollment to the trial is feasible (i.e., enrollment >66% of eligible participants), surgeons are not willing to enroll patients requiring complex resections and that the trial may miss patients that have their primary tumour resected outside the trial institution. Our study also showed that population-based databases can help identify 50% more eligible participants for this specific trial, suggesting that these databases can be used as an adjunct to traditional methods of participant accrual.

METHODS AND ANALYSIS

Traditional methods of patient accrual as well as population-based histopathology and radiology datasets will be used to identify eligible patients diagnosed with synchronous primary colorectal cancer and liver metastases at 10 Canadian institutions. Patients will be centrally randomized using a concealed, computer-generated schedule in a 1:1 ratio to simultaneous (i.e., intervention) versus staged (i.e., control) resection of the primary tumour and the liver metastases and stratified according to degree of complexity of colorectal resection (high versus low) or the extent of the liver resection (major versus minor). The primary outcome will be overall survival. Secondary outcomes will include the following: 90-day postoperative complications; length of hospital stay**;** quality of life; and progression-free survival. The planned sample size is 170**.**

ETHICS AND DISSEMINATION

This study will be approved by each institution's research ethics board after registration at www.clinicaltrials.gov. This study has the potential to change clinical practice in the management of patients with synchronous colorectal cancer liver metastases. Results will be available to the public via presentation at international conferences, social media, peer review journal publication as well as direct feedback to the participants of the study.

KEYWORDS: synchronous colorectal cancer liver metastases, overall survival, postoperative complications, comprehensive complication index, postoperative mortality

Highlights

- Previous pilot trial suggested that enrollment to a trial of simultaneous resection for colorectal cancer liver metastases is feasible (enrollment of >66% of eligible participants). A previous randomized trial suggested similar postoperative

complications between simultaneous and staged resections and a trend to improved overall survival with simultaneous resection.

- A trial of simultaneous resection may miss patients that are not referred to the trial institution. Also, surgeons will not include patients requiring major hepatectomies and complex colorectal resections. Population-based datasets can identify 50% more eligible patients for this trial and could be used to increase participant accrual.
- A randomized trial with adequate sample size is needed to better evaluate the role of synchronous resection on patient overall survival and postoperative complications.

1. BACKGROUND AND RATIONALE

Patients with colon cancer and synchronous liver metastases are candidates for cure by resecting the primary tumour and the liver metastases.(1-6) Patients able to undergo complete margin-negative resection are anticipated to have a 5-year overall survival of 50%, with or without the administration of adjuvant chemotherapy.(4, 7, 8)

Synchronous colorectal cancer liver metastases, defined as the diagnosis of liver metastases at the time of primary colorectal cancer presentation, occur in 20% of patients with colorectal cancer.(9) The appropriate timing of liver and colorectal resection among patients who present with synchronous disease has not been standardized. Some surgeons perceive potential advantages to the simultaneous approach, including a shorter length of hospital stay, and the need for only one operation; while other surgeons worry of a higher postoperative complication rate and postoperative mortality with the simultaneous approach, as well as a higher complexity to organize and schedule a simultaneous resection

in their institutions.(3, 10) Overall, surgeons have increased the use of simultaneous resection over recent years; with approximately 35% of patients with synchronous disease undergoing simultaneous resection, most such cases requiring minor liver resections and simple colorectal resections.(3, 11) Alternatively, surgeons can provide a staged approach, in which the primary tumour is resected first, followed by the liver metastases (i.e., primary first approach), an approach that has been suggested for patients that require an urgent operation for the primary tumour (i.e., bleeding or obstruction) or for patients who require a complex colon resection. The third approach for the management of patients with synchronous disease is to resect the liver metastases first, followed by the primary (i.e., liver first approach), based on a recently published observational study supporting this approach for patients with rectal cancer that require radiation therapy and have multiple bilobar liver metastases.(12-14) This recent large retrospective cohort study suggested that the "liver first" approach improves overall survival for patients with bilobar liver metastases, likely due to the higher risk of liver disease progression and unresectability in those patients who wait longer to have their liver resection.(14)

Multiple retrospective cohort studies have suggested similar postoperative complications between the simultaneous and staged approach, lower length of hospital stay in the simultaneous group and consequently lower costs for the health care system.(3, 11) Comparison of overall survival between groups had been explored before, however, due to the lack of prospective data analysis, results have been variable.(3, 15) Therefore, there is equipoise regarding the timing of liver and colorectal resection for patients with synchronous disease. Of note, a survey performed among colorectal and hepatobiliary

surgeons suggested that most surgeons believe simultaneous resection is feasible for patients with simple liver and colorectal resections.(10) Data and therefore, support for simultaneous resections in patients who require major hepatectomies (i.e., three or more liver segments),(16) or complex colorectal resections (i.e., defined as a colorectal resection that requires more than 6 hours to complete) is not clearly defined.(10, 17)

A recent randomized controlled trial comparing simultaneous versus staged resections enrolled 105 participants, of which, 85 were analyzed, confirmed prior reports from observational studies and suggested a similar major postoperative complication rate between groups (49% for the simultaneous approach versus 46% for the staged approach). Results from the secondary objectives of the trial suggested a shorter length of hospital stay for the simultaneous group (median 7 days) compared to the staged group (median 17 days, p=0.002) and a trend towards worse disease-free survival and overall survival for the staged group (estimated 2-year overall survival 86% in the simultaneous group versus 75% in the staged group). However, the trial took over 10 years to accrue and included a small number of participants, with an even smaller number requiring complex resections. This trial was powered to detect a difference in postoperative complications and not powered to detect differences in overall survival. (17) The authors of this study suggested that a delay to liver surgery may have made liver resection not feasible due to progression of liver disease. They also explain that their trial took longer than expected as most potentially eligible participants they screened, already had their primary resected elsewhere, therefore they were not eligible for the trial and not enrolled.

Our group recently published the results of a multi-institutional pilot single arm feasibility trial of simultaneous resection.(18) We demonstrated that enrolling patients to a trial of simultaneous resection is feasible based on the eligibility criteria of the trial, which included complex colorectal resections and major liver resections. We also noted that postoperative complications in those undergoing simultaneous resection, although higher compared to liver only resection (historical control)(3), were acceptable (41% versus 24%) given the low mortality rate (<5%) and the fact that this proportion of postoperative complications is likely to be comparable the addition of the complications from two separate procedures (i.e., staged resection).(17) Although length of hospital stay of enrolled participants was longer than the results of the randomized trial (10 days versus 7 days), median disease free survival of enrolled participants was 16 months, after median follow up of 25 months, a finding that is consistent with previously published data.(19) Overall survival at 2 years was 79%, 95% CI 63 to 98, similar to the survival data of the recently published randomized controlled trial.(17)

As an attempt to identify alternate methods to recruit patients with cancer to surgical clinical trials, this feasibility trial was performed alongside (same timeline) another study that determined the total number of patients diagnosed with synchronous colorectal cancer liver metastases in the region (population 1.4 million), using population-based electronic datasets of pathology reports and imaging. This study found that the use of population-based methods was able to identify 50% more eligible participants for the RESECT trial compared to traditional methods of enrolment. Considering that 70% of eligible participants identified via traditional methods were eventually enrolled in the RESECT trial, it is possible that using

population-based accrual methods, the number of participants enrolled could have been much greater, if for example, potential participants were approached via their treating physician prior to resection of their primary tumour.

Given the need of a properly sized trial, for select patients with synchronous colorectal cancer liver metastases, we have designed a randomized trial comparing simultaneous to staged liver resections with overall survival as the main outcome of interest. The lessons learned from our previous studies, have assisted us to define the inclusion and exclusion criteria, the primary outcome of interest, the sample size, and the accrual methods of enrollment. Now is the best time to perform this trial as there is equipoise and a high level of interest in the surgical and medical oncology community regarding timing of colorectal and liver resection in these patients.

1.1. *Study Objectives:*

1.1.1. General Objective: To improve the long-term outcome of patients diagnosed with synchronous colorectal cancer liver metastases.

1.1.2. Primary Objective: To compare the overall survival between groups.

1.1.3. Secondary Objectives: (1) To compare the postoperative complication rate at 90 days following index surgery or surgeries, (2) to determine differences between groups in global health related quality of life (QoL) at three months following index surgery or surgeries (3) to compare length of hospital stay between groups and, (4) to compare the progression-free survival between groups.

2. METHODS AND ANALYSIS

2.1. Study Design: A multi-centre, parallel, 1:1, unblinded, superiority, controlled randomized clinical trial (Figure 1).

2.2. Study Setting: This trial will be performed at 10 tertiary care hospitals in Canada.

2.3. Patient Population:

2.3.1. Inclusion Criteria: Adults who are medically fit for resection according to treating physician, presenting with resectable, synchronous, biopsy proven colorectal cancer liver metastases (i.e., adenocarcinoma in the primary tumour or the liver). For study purposes, patients that meet the inclusion criteria for the trial are defined as potentially eligible participants.

2.3.2. Exclusion criteria: confirmed extrahepatic metastatic disease, tumours treated with local transanal excision, patients requiring two-stage liver resection and patients with prior liver resection. Patients requiring resection of more than 5 liver segments or with an estimated future liver remnant <30%. Patients requiring intraoperative bile duct resection and reconstruction. Patients requiring both major liver resection (i.e., 3 or more segments) and complex colorectal resection (i.e., predicted operating room time >6 hours). Additionally, pregnant, or lactating female patients will be excluded.

Eligible participants are those patients meeting the inclusion criteria and not meeting any of the exclusion criteria.

Major liver resection was defined as resection of three or more liver segments.(16) We defined complex colorectal resection as a colon or rectal resection with a predicted operating room time >6 hours. This latter time interval was based on data

from our pilot trial.(18) In the feasibility study, we identified participants that had at least one high-risk composite outcome (i.e., anastomotic leak, postoperative death, extended length of hospital stay >17 days and estimated blood loss >1100 mL). We noticed that participants meeting these high-risk criteria (n=20) had similar baseline characteristics to those that did not meet these high-risk criteria (number of liver lesions, location of the primary tumour, type of liver or colon surgery required), however they had a significantly longer operating room time for the colorectal portion of the case (75^{th} percentile: 6 hours). Assuming that surgeons are very accurate in predicting the estimated length of operating room time required to perform an operation, we decided to base the definition of complex colorectal resection on the surgeon's predicted operating room time.

2.4. Study Intervention: Participants will undergo simultaneous resection of the colon or rectum and liver within 4 weeks of randomization once the decision to proceed with surgery has been made (i.e., following completion of neoadjuvant chemotherapy or radiation therapy) (Appendix 1). The choice of surgeon will be determined by standard of care (i.e., colorectal surgeon, hepatobiliary surgeon, general surgeon. We ask that the surgery (or surgeries) be performed at the trial institution. Our feasibility trial demonstrated large variability between centres in the preoperative management of participants (i.e., administration of neoadjuvant chemotherapy, number of cycles, type of drugs utilized). Therefore, this trial will aim to be pragmatic in the way patients are managed around the time of surgery, as long as the randomization schedule is preserved. The time from last

chemotherapy dosing and surgery should be at least 4 weeks. Adjuvant chemotherapy can be administered after surgery or not at all, depending on each institution's standard. Resectability of the liver lesions will be defined by the standard of care of each institution after discussion at multidisciplinary care conferences. A CT scan of the chest, abdomen, and pelvis with intravenous contrast within 6 weeks of resection will be required for each participant. It is recommended that a resectable patient should have an estimated future liver remnant ≥30% and if participants received neoadjuvant chemotherapy with FOLFOX or FOLFIRI, or if they have cirrhosis, then the estimated future liver remnant should be ≥40%. It is also recommended that following liver resection, there must be at least one major outflow (i.e., hepatic vein), inflow (i.e., portal vein and hepatic artery) and biliary drainage preserved. The type of liver resection will be described according to the Couinaud classification and the Brisbane terminology of liver anatomy(16). The type of colorectal and liver resection as well as the use of minimally invasive techniques (i.e., robotic, or laparoscopic surgery) will be decided by the treating physician. It is recommended that a low central venous pressure be maintained in order to decrease intraoperative blood loss, [5,6] and that liver resection be performed prior to colorectal resection in order to keep a low central venous pressure during that part of the case. Anesthesia, use of inotropes, and intraoperative fluid management, blood transfusions, use of drains or diverting stomas, and postoperative care, including pain control, removal of indwelling catheters will be determined by each institution's standards.

Participants in the control group will undergo colorectal resection and liver resection in two separate anesthetic settings with a planned second resection between 4 to 12 weeks, without administration of chemotherapy or radiation therapy between surgeries. The order of surgeries can vary (i.e., liver, or colorectal resection first) depending on surgeon's preference.

2.5. *Outcomes*

2.5.1. *Primary Outcome*: overall survival measured from the time of randomization to the time of death from any cause.

2.5.2. Secondary Outcomes: (1) 90-day postoperative complications measured using the Clavien-Dindo score and the comprehensive complication index,(20, 21) (2) global health-related QoL using the EORTC questionnaire,(22, 23) (3) length of hospital stay measured following each index operation to the day of discharge, (4) progression-free survival measured from the time of randomization to the time of disease recurrence or death from any cause.

Postoperative complications for staged procedures will be measured separately and added to create a total. Length of hospital stay for staged procedures will also be added to create a total. Recurrence will be defined as evidence of recurrent colorectal cancer, including new primary colorectal cancer, diagnosed by the treating physician based on standard of care imaging (CT scans, ultrasounds, MRI scans, or FDG-PET-CT scans), pathological reports of biopsies or specimens and CEA levels. Type of recurrence will be classified as local recurrence of the primary tumour, recurrence in the liver, lung and other (i.e., retroperitoneal lymph nodes, brain, etc.).

2.6. *Participant Timeline and Study Data Collection:*

Baseline participant demographics will be collected from hospital charts, or electronic medical record and transcribed onto electronic case report forms the day of randomization during the clinic visit in person or by phone (Appendix 1). Baseline QoL questionnaires will be obtained from participants following the first clinic visit (Table 1). We strongly recommend, based on prior feasibility studies suggesting participant burnout with prolonged research clinic visits, to limit the baseline assessment to the consent process (i.e., 15 minutes), and delaying the completion of the baseline assessment (demographics, QoL questionnaires, etc.) to a different clinic visit or phone appointment. The next assessment will occur the day of surgery and on postoperative day 2, 5 and day of discharge, in which, information on postoperative complications will be collected from participants' hospital records (see secondary outcomes). Following discharge from each index operation, participants will be followed in person or by phone at 4 weeks ($\pm$ 1 week) and at 12 weeks ($\pm$ 2 weeks) to collect QoL questionnaires and any postoperative complications that happened after discharge, including emergency room visits or unplanned hospitalizations. Data on administration of preoperative and postoperative chemotherapy will be collected. Participants then will be followed for two years following randomization every 6 months. Standard of care imaging can vary between institutions, but it is recommended to be performed every 6 months. Survival information will be collected from clinical notes, obituaries, or communications with treating physicians.

2.7. *Sample Size Justification and Feasibility:*

Based on information from our previous pilot study and a previously published randomized controlled trial, the median survival time on the control arm was 46 months. Assuming the hazard ratio for death of control subjects relative to experimental subjects is 2.31, a three-year accrual period and additional follow-up of 2 years, we will require 71 participants per arm to be able to reject the null hypothesis that the experimental and control survival curves are equal with a power of 80% and a type 1 error of 0.05. Our data shows that approximately 80% of participants assigned to the intervention group will undergo simultaneous resection (due to intraoperative complications or intraoperative findings of progression of disease), therefore, our sample size is increased to 170 participants (85 per arm).

2.8. *Recruitment:*

Participants will be recruited based on each institution's standards, including identifying patients with colorectal cancer and liver metastases by screening all patients referred to the surgical clinics of hepatobiliary and colorectal surgeons. We recommend advertising the study to the oncological community near the trial institution by sending letters, faxes and emails to surgeons, medical oncologists, and gastroenterologists. It is also recommended to identify potentially eligible participants (i.e., patients meeting the inclusion criteria) via cancer multidisciplinary case conferences, by hanging posters and flyers in surgeons and oncologists' clinics, and by presenting this protocol at national and international meetings and their respective social media platforms. We suggest that each institution's principal investigator promote this trial using their own social media platform with trial approved visual abstracts, which although not tested in the original RESECT trial,

is the new way of disseminating information across participating sites. Our feasibility study showed that 67% of all eligible participants can be recruited using these traditional methods of accrual, with a recruitment rate of 1 participant per month per institution.

Based on the lessons learned from our feasibility studies, research assistants should communicate directly with surgeons prior to patient's clinic visit the RESECT-trial, to identify patients that could become potential participants (i.e., once the decision to proceed with surgery has been made). Once a patient is confirmed to meet the inclusion and exclusion criteria (except the planned surgery), they should be approached during this first clinic visit, even if the surgeon does not have a surgery date planned. This first interaction with the research staff will help the research staff become familiar with the patient and to notify them as soon as they are eligible to participate in the trial (i.e., once the plan for surgery has been made by the surgeon). The early identification of potential participants is important as we learned from the feasibility trial that scheduling a date for simultaneous resection is complex and requires several weeks of planning. Often, the surgery is performed by two different surgical specialists (i.e., colorectal and hepatobiliary), leading to delays in surgery if a patient is randomized to the staged approach without sufficient time to schedule the surgery. Delay in surgery date due to conflicts with a clinical trial is sometimes inevitable, but it should be avoided as much as possible to prevent patient harm, preserve a good relationship with the surgeon, the participant, and the hospital administration. If a participant is randomized to the staged approach, the surgery is usually booked within 2 to 4 weeks.

Since our feasibility study suggested we can identify 50% more eligible participants for the RESECT trial using population-based databases, we will dedicate specific research

personnel to identify and recruit eligible participants via these population-based databases in eligible hospitals (those that have available datasets to them). All hospital and clinic pathology reports related to cancer from each health administrative region across most Canadian provinces (Ontario, Quebec, British Columbia, and Alberta) are collected and codified in real-time (i.e., as soon as the report is available on the patient's institution's medical record). For example, in Ontario, this database is called the e-PATH electronic database at Cancer Care Ontario (the agency overseeing the quality of cancer services in Ontario). Each Ontario region has a diagnostic imaging repository (i.e., OneView for Southwest Ontario). Each diagnostic imaging repository is an electronic repository of radiology reports and imaging (e.g., CT and MRI scans) done at each hospital in Ontario. Each institution's research assistant will prospectively review the electronic pathology database (e-PATH) biweekly to identify patients diagnosed with colorectal cancer by endoscopic or percutaneous biopsy. Imaging reports of those patients will be reviewed using diagnostic imaging repository networks (i.e., OneView for Southwest Ontario). A research assistant will identify patients with liver metastases and exclude those that meet exclusion criteria for this study (i.e., pregnant patients, diffuse extrahepatic disease), patients with previous liver resection or with their primary tumour already resected. The final list of potentially eligible participants will be reviewed by the principal investigator of each institution every two weeks to determine eligibility for the trial (i.e., resectability). Patients that meet eligibility for this trial will be approached for trial participation after confirmation with their treating physician is obtained that they have discussed the trial with their patients and that the research team can approach them to discuss this trial. A log of potentially

eligible, eligible, and enrolled participants identified via population-based methods and traditional methods will be kept.

2.9. *Randomization:*

Randomization will be conducted by the Ontario Clinical Oncology Group, an academic Clinical Trials Unit in Hamilton, Ontario. The randomization scheduled will be computer-generated and stratified according to degree of complexity of the combined resection (high versus low). The degree of complexity of the resection will be based on the complexity of colorectal resection (high versus low) or the extent of the liver resection (major versus minor). Major liver resections are defined as liver resections of $\geq$ 3 liver segments.(16, 24) Complex colorectal resections are defined as those requiring >6 hours to complete. If a patient requires a complex liver resection or a complex colorectal resection, then that patient will be categorized as a complex resection. Each institution's research coordinator will contact the Ontario Clinical Oncology Group for randomization after patient signs consent and will notify the treating physician the allocation group. Allocation will be concealed.

2.10. *Data Management, Trial Organization and Quality Assurance:*

2.10.1. *Steering Committee:*

The principal investigator and three co-investigators will form the steering committee for this study and will meet prior to the study start-up, and every 4 months. They will be responsible for monitoring patient safety throughout the study. Members are experts in the fields of clinical trials methodology, oncology and surgery and will receive study data pertinent to patient safety at the midpoint of patient accrual.

2.10.2. *Central Adjudication Committee:*

Two professionals that are experts in the medical field who are outside of the research team will be responsible for assessing data on disease recurrence and postoperative complications for each patient per de-identified source documents.

2.10.3. *Coordinating Methods Centre:*

The Ontario Clinical Oncology Group will perform data management and statistical analyses. In addition, provide methodological and administrative support to all committees, investigators, and study personnel.

2.11. *Statistical Analyses:*

All outcomes will be compared according to randomization group (intention-to-treat analyses). Participant demographics will be reported as proportions and absolute counts or median and interquartile range as appropriate. Overall and progression-free survival will be estimated with Kaplan Meier methods and compared with a log-rank test. The treatment effect will be summarized by the hazard ratio with its associated 95% CI for the intervention group relative to the control group and estimated from an unadjusted Cox proportional hazards model. Statistician will be blinded for the primary outcome assessment. Proportions of postoperative complications will be compared using chi-square test. Median comprehensive complication index will be compared using the Kruskal-Wallis test. Changes in the continuous QoL outcomes from baseline to second postoperative visit (i.e., 90 days post index surgery or surgeries) will be summarized using mean and standard deviation and compared with independent t-test. Differences in length of hospital stay between groups will be compared using Kruskal-Wallis test. All p-values will be 2-sided and values of less than 0.05 will be considered statistically significant.

3. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the recommendations adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964. A centralized research ethics board will approve the study protocol and documents in Ontario prior to commencement. Other provinces in Canada will have their own institution's research ethics board approve the study prior to initiation. Written informed consent will be obtained from all participants prior to enrollment.

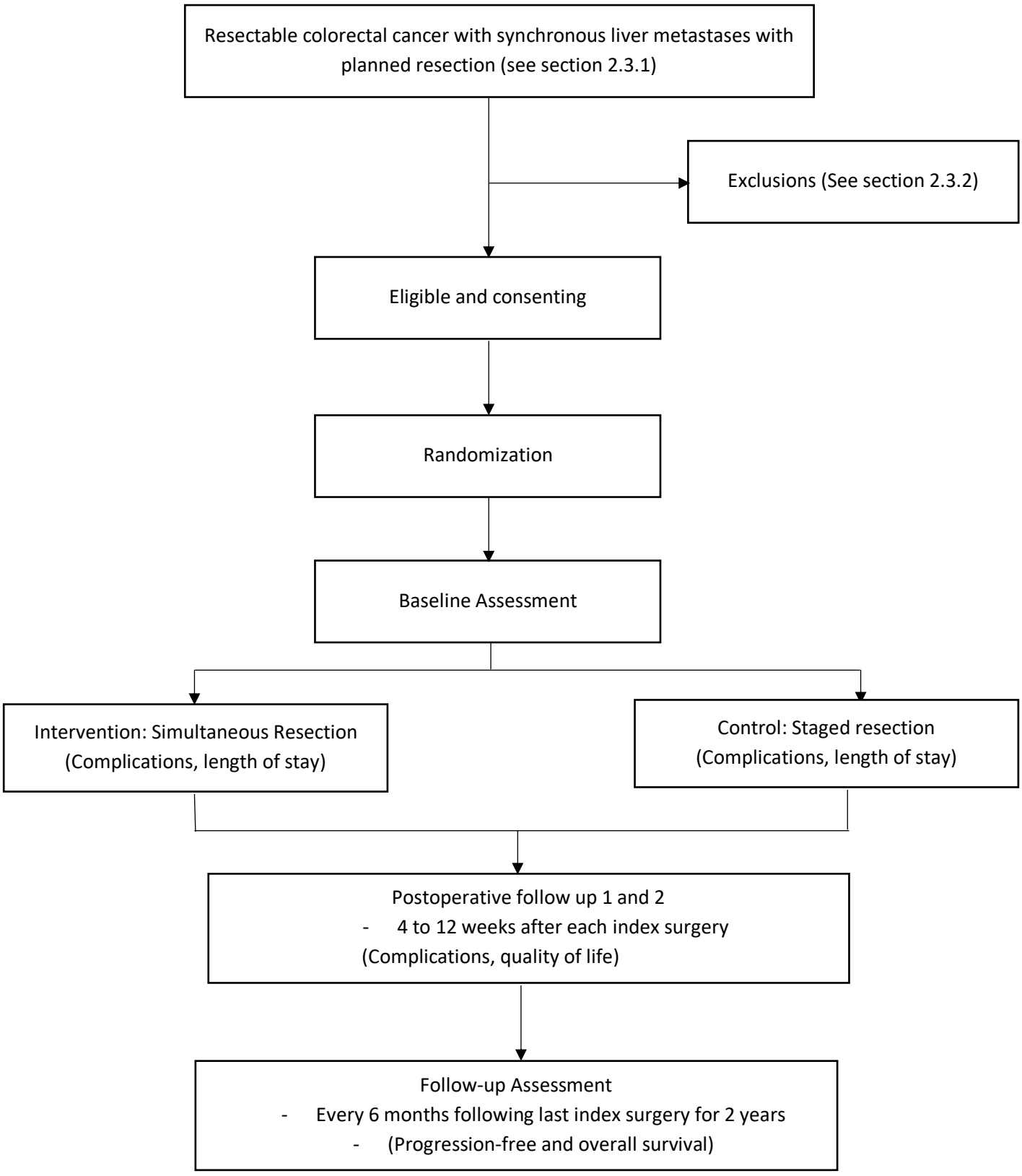
4. SIGNIFICANCE

Approximately 35% of patients with synchronous colorectal cancer liver metastases undergo simultaneous resection of the primary tumour and liver metastases, while the rest, undergo staged resections. Most of these patients undergoing simultaneous resection require a simple liver and a simple colorectal resection. Data on patients requiring either a complex liver or a complex colorectal resection is still unknown. There is data suggesting that although postoperative complications may be similar between groups, overall survival might be better for the simultaneous group, mostly due to progression of disease in the staged group.

We believe, based on surgeon survey and available data that there is sufficient clinical equipoise to support a well-designed, randomized controlled trial addressing these questions. This study will provide the necessary data to make an informed decision on simultaneous versus staged resection for these patients.

The recruitment strategy utilized for this trial will help researchers familiarize themselves with population-based databases, and to test their ability to recruit participants to surgical cancer trials**.**

FIGURE 1 – STUDY SCHEMA



	APPENDIX 1 – SCHEDULE OF STUDY PROCEDURES						
Study Procedure	Screening	Baseline Assessment	Day of Surgery (repeat if staged approach)	Postoperative day 1, 3 and 5 (repeat if staged approach)	Postoperative follow-up 1 and 2 (repeat for control)	Post-randomization follow-up 1- 4 (repeat for control)	End of Study
Informed Consent	X						
Biopsy	X						
Imaging (CT or MRI)	X					X	
Pregnancy test (b-HCG)	X						
Randomization	X						
Demographics		X					
Quality of Life questionnaire		X			X		
Medical History		X			X	X	
CBC, PTT, INR, chemistry		X		X	X	X	
CEA		X				X	
Postoperative Complications				X	X		
Disease progression						X	
Survival						X	
Study Termination							X

5. REFERENCES

1. Committee CCSA. Canadian Cancer Statistics 2019. Canadian Cancer Society. 2019.
2. Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev. 2015 Nov;41(9):729-41.
3. Bogach J, Wang J, Griffiths C, et al. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cohort study. Int J Surg. 2020 Feb;74:68-75.
4. Kanemitsu Y, Shimizu Y, Mizusawa J, et al. Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2021 Sep 14:JCO2101032.
5. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018 Jul;16(7):874-901.
6. Engstrom PF, Arnoletti JP, Benson AB, 3rd, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw. 2009 Sep;7(8):778-831.
7. Serrano PE, Gu CS, Husien M, et al. Risk factors for survival following recurrence after first liver resection for colorectal cancer liver metastases. Journal of surgical oncology. 2019 Oct 14.
8. Kim HS, Lee JM, Kim HS, et al. Prognosis of Synchronous Colorectal Liver Metastases After Simultaneous Curative-Intent Surgery According to Primary Tumor Location and KRAS Mutational Status. Ann Surg Oncol. 2020 Dec;27(13):5150-8.
9. McMillan DC, McArdle CS. Epidemiology of colorectal liver metastases. Surg Oncol. 2007 Jul;16(1):3-5.
10. Griffiths C, Bogach J, Simunovic M, et al. Simultaneous resection of colorectal cancer with synchronous liver metastases; a practice survey. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2020 May;22(5):728-34.
11. Wang J, Griffiths C, Simunovic M, et al. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cost analysis in Ontario, Canada - Health economic evaluation. Int J Surg. 2020 Jun;78:75-82.
12. Ayez N, Burger JW, van der Pool AE, et al. Long-term results of the "liver first" approach in patients with locally advanced rectal cancer and synchronous liver metastases. Diseases of the colon and rectum. 2013 Mar;56(3):281-7.
13. Buchs NC, Ris F, Majno PE, et al. Rectal outcomes after a liver-first treatment of patients with stage IV rectal cancer. Annals of surgical oncology. 2015 Mar;22(3):931-7.
14. Giuliante F, Vigano L, De Rose AM, et al. Liver-First Approach for Synchronous Colorectal Metastases: Analysis of 7360 Patients from the LiverMetSurvey Registry. Annals of surgical oncology. 2021 Dec;28(13):8198-208.
15. Wang LJ, Wang HW, Jin KM, Li J, Xing BC. Comparison of sequential, delayed and simultaneous resection strategies for synchronous colorectal liver metastases. BMC surg. 2020 Jan 17;20(1):16.

16. Bismuth H, Chiche, L. Surgery of hepatic tumours. Prog Liver Dis. 1993;11:269-85.
17. Boudjema K, Locher C, Sabbagh C, et al. Simultaneous Versus Delayed Resection for Initially Resectable Synchronous Colorectal Cancer Liver Metastases: A Prospective, Open-label, Randomized, Controlled Trial. Ann Surg. 2021 Jan 1;273(1):49-56.
18. Serrano PE, Parpia S, Karanicolas P, et al. Simultaneous resection for synchronous colorectal cancer liver metastases: A feasibility clinical trial. Journal of surgical oncology. 2021 Dec 8.
19. Serrano PE, Gu CS, Husien M, et al. Risk factors for survival following recurrence after first liver resection for colorectal cancer liver metastases. J Surg Oncol. 2019 Dec;120(8):1420-6.
20. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205.
21. Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Annals of surgery. 2014;260(5):757-63.
22. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.
23. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. Journal of clinical epidemiology. 1997;50(4):441-50.
24. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg. 2013 Mar;257(3):377-82.

Chapter 6. Conclusions and Future Directions

6.1 Thesis Summary

In this doctoral thesis we explore methodological challenges often encountered in surgical clinical trials that can result in slow recruitment and early trial discontinuation. As evidenced in the literature, slow recruitment is the most common reason for discontinuation of clinical trials, including surgical trials. This thesis builds on the existing literature by proposing a framework for understanding the different areas in the development of surgical trials that can affect recruitment, providing examples of issues that affect it, and proposing unique strategies to improve accrual to cancer surgical clinical trials.

The studies presented in this thesis are carefully designed based on our framework and exemplify the two main types of surgical clinical trials; the PROGRESS trial (Chapter 2) compares a medical intervention on patients undergoing surgery, while the RESECT trial (Chapter 3), investigates a surgical intervention considered to be a surgical innovation (i.e., simultaneous resection of colorectal cancer liver metastases). At the end of each published study, a separate section applies our framework to facilitate the exploration of challenges to participant recruitment and possible solutions to each challenge. In this manner, each challenge represents an opportunity for improvement. One of these opportunities is presented as a separate chapter (Chapter 4) which explores the role of population-based databases in the recruitment process to clinical trials in surgery. Moreover, Chapter 5 draws on lessons learned from the previous studies to design a protocol for a large randomized controlled trial in cancer surgery (RESECT-RCT).

6.2 Lessons Learned from this Thesis

6.2.1 Lessening the burden to the clinician surgeon

Although not unique to cancer surgery trials, the challenges and opportunities that are presented in this thesis are particularly salient for clinical trials of patients undergoing surgery for cancer. Surgeries for cancer are considered urgent; there is always a rush to get the patient to the operating room as soon as possible to prevent progression of disease that could render a patient unresectable. Since clinical trials are not part of the standard component of a patient's clinical care pathway, they may be perceived as causing unnecessary delays to treatment. Traditionally, it is the role of the surgeon and other physicians in the patient's circle of care to notify the research team of a potential participant after they have introduced the clinical trial to their patient. However, it is common that surgeons and other staff in the patient's circle of care may not remember or may not have the time or initiative to notify the research team about a potential new trial participant in a timely manner, leaving little opportunity to enroll patients in surgical clinical trials that require a long preoperative window (such as the PROGRESS trial) or that require a complex operative schedule (such as the RESECT trial).

While performing the trials, our team developed several strategies to expedite the early identification of potential participants, such as the use of population-based datasets, and the identification of potential participants prior to their appointment with surgeons, even before the determination of surgical candidacy.

Although most physicians and surgeons agree that they feel comfortable discussing clinical trials with their patients, only a small proportion of them refer patients to studies.(Rahman et al., 2011) The issue of poor referral was clear to us while performing

the RESECT clinical trial. We learned that by using traditional methods of trial enrollment (i.e., relying on surgeons or physicians to refer patients to the research team), we were missing many potential trial participants. This was evident when reviewing the results of the population-based database study, which indicated that many potential participants were undergoing colorectal resection first, then referred later for liver resection, at which point they were ineligible for the RESECT trial (Chapter 4). Many studies have suggested the use of pamphlets, posters, mass communications to surgeons, brochures, or tags in patients' electronic or physical charts to remind physicians of trials their patients may be eligible for. Yet, none of these methods have been shown to substantially improve recruitment rates.(Treweek et al., 2013) This suggests that although surgeons and physicians understand the importance of clinical trials, there are certain barriers that limit recruitment of their patients, most importantly, "time constraints".(Spaar et al., 2009) Therefore, research team members play a critical role in identifying potential participants, discussing with surgeons potential eligibility to trials, and establishing a relationship with potential participants as early as possible.

Patients are more likely to participate in surgical clinical trials if their surgeon discusses the options for trials with them, especially if the surgeon underscores the importance of the clinical trial (i.e., explaining equipoise and uncertainty of current treatment strategies).(Arnaout et al., 2016; Kaas et al., 2005) However, current literature suggests that clinicians often do not inform patients of trial opportunities.(Kaas et al., 2005) Surgeons frequently forget or are unaware of trial options when they meet with patients; moreover, even when aware of a trial, surgeons may not be familiar with eligibility criteria.

Since we know that surgeons are interested in clinical trials for their patients but encounter important barriers in communicating these options with patients, it is imperative to explore strategies to fill this communication gap.

During the development of the clinical trials included in this thesis, we also learned that participant identification was substantially better when the research team collaborated with the surgeon to discuss potential trials available *prior* to the surgeon meeting their patients. To do so, we had a research coordinator present in the surgical clinics alongside the surgeon. Prior to the surgical clinic visit, research staff discussed with surgeons and their assistants the new patients that were referred to their practice for potential surgical candidacy. Surgeons commonly know if a patient is a potential surgical candidate or not based on the referral that was sent to them, which typically includes pathological diagnosis and imaging. This allowed research staff to meet with potential trial participants from the beginning of their surgical journey, even prior to determining surgical eligibility. By identifying patients early in their cancer journey (i.e., the first time they meet the surgeon) and establishing a relationship with the patient, patients and surgeons were aware of possible surgical trials from the beginning, even if the patient did not end up having surgery. Once the decision to proceed with surgery was made, the research team discussed in detail the trial and consent process with the patient.

Even though, the task to identify potential participants may be delegated to the research staff, the role of the surgeon in the research process is still very important. The surgeon needs to: 1) be willing to discuss various trial options for their patients with the research team; 2) communicate to their patients the potential trial opportunities and obtain

verbal consent for research staff to approach them for a trial; and perhaps most importantly 3) support their patients if they wished to proceed with a clinical trial, as patients often rely on the opinion of their treating physician when deciding to participate in a clinical trial.

It is our firm belief that treating physicians and surgeons should continue to occupy a central role in the execution of surgical clinical trials; however, several key barriers identified in this thesis suggest that they should not be responsible for the identification and referral of potential participants to a research study. These recommendations bypass the need for the surgeon to identify and refer potential participants to clinical trials, while simultaneously recognizing their critical role in the recruitment process, empowering surgeons to make informed clinical trial decisions in an efficient and timely manner. We strongly believe that recruitment can be improved by empowering referring physicians and surgeons to become better integrated into research teams, while simultaneously limiting their time commitment and responsibilities.

Several important limitations with these two methods of patient identification and recruitment were identified. Most importantly, none of these "accrual strategies" were randomized, therefore we lack the ability to determine their utility to increase recruitment to a clinical trial. One way to test these strategies would be to perform a cluster randomized trial design, in which one centre is randomized to a specific recruitment strategy while a different centre is randomized to another one. Secondly, by screening all potential participants without confirming if they are eligible for surgery, the workload for the research team was higher, which may not be feasible for research teams that are already small and "stretched out" to their maximum capacity. Therefore, this strategy is only

feasible for research teams that have the financial and physical capacity to do so. Thirdly, often there was not enough physical space in the surgical clinics for the research staff to spend time with multiple potential participants, leading to potential trial participants being missed. Potential solutions to the issue of physical space are presented in the following section (6.3.2 Superimposing research infrastructure into the clinical setting).

6.3 Future Directions

Some strategies to improve recruitment were identified but were not performed in this thesis and are therefore suggested here as future directions.

6.3.1 Use of population-based databases to identify and contact participants

Although the use of population-based datasets was able to identify 50% more eligible patients for the RESECT trial, it is not known whether these patients would have enrolled in the trial. Our next steps are to test the use of population-based datasets in the recruitment of patients to a surgical clinical trial, as proposed in the RESECT-RCT protocol (Chapter 5).

6.3.2 Superimposing research infrastructure into the clinical setting

Incorporating research staff into the surgeons' clinics was not straightforward. The physical space in the clinic is often limited and the time allocated to each patient is narrowly defined. Surgical clinics are designed with the clinician as the top priority and research staff usually takes second place. Adding research staff to the clinic meant that patients would spend more time in the examination room, thereby delaying clinic visits for other patients that were scheduled to be seen by surgeons at that time. This impacted the dynamics of the

surgical clinics, and the research staff was therefore not welcomed. As such, we propose several key adaptations:

1) Physical space constraints can be alleviated by using virtual meeting spaces (i.e., research staff can introduce themselves in clinic and follow-up with potential participants virtually). As both health care providers and patients have adapted to meet virtually amid the COVID-19 pandemic, there are some opportunities to further explore the integration of virtual spaces for research purposes.(Borycki & Kushniruk, 2022; Sim et al., 2020) Improved support from surgeons could result in discussions between research staff and potential participants at subsequent virtual visits.

2) To use alternate clinical spaces for research purposes. Multidisciplinary cancer conferences are prospective meetings that are used to discuss diagnoses and treatment plans for patients with cancers. Although not all patients with cancer are reviewed in these meetings, those with complex cancers that require the input from different specialties are typically reviewed. These meetings are usually attended by a variety of subspecialists, including surgeons. Most times, these meetings are not attended by research staff with the purpose of identification and screening of potential participants; however it is possible that these meetings can be used for that purpose as long as privacy and confidentiality are preserved, and patients are informed.(Fahim et al., 2020) Currently, most multidisciplinary cancer conferences are performed virtually, or have a virtual option, therefore obviating the need for physical space dedicated to the research staff. Some centres have adopted a pre-visit multidisciplinary evaluation to all patients referred for a specific type of cancer that typically requires input from different specialists (i.e., radiation oncology, medical

oncology, and surgery). Having a research staff present at these meetings helps identify potential research studies that these patients may be eligible for in a timely manner.

3) To build physical space dedicated to research within the clinical setting. While this is the preferred option, we acknowledge it may not be feasible given resource constraints.

6.3.3 Involving patient partners in the research plan

Although not utilized during the development of this thesis, patient partners can aid in recruitment in different manners and in different stages of the study preparation. Many times, researchers avoid patient and public involvement in their research if it is not required by the granting agency. This could be because there is paucity of data on how to operationalize effective patient and public involvement in research, hindering their inclusion in clinical trials.

The concept of patient partners refers to individuals who have been patients, caregivers, or family members of patients that have some degree of expertise in patient experience and can therefore be engaged in research. They can be involved from the time of trial design through the activation, accrual, and data analysis. Based on the framework presented in this thesis, patient partners can identify potential issues for recruitment from the development of the study population of interest, to the study intervention (including blinding methods), to the feasibility of such study in the local population.(Tomlinson et al., 2019) They can also help with the consent process and can support the research program with participant recruitment by providing insights into how the research may affect intended participants, suggesting areas in which barriers to recruitment can be decreased.

6.4 Final Comments

The challenges and opportunities presented in this thesis will help investigators mitigate recruitment issues when designing a trial, and this thesis contributes to existing literature by proposing a framework developed based on examples from several surgical trials. Although the recruitment challenges explored in this thesis are not new, the synthesized manner in which they are presented, and the proposed mitigation strategies to overcome these challenges, are innovative. This systematic approach to assess a clinical trial prior to its development can be used by surgeon investigators to improve the quality of their trial design and execution.

References

Arnaout, A., Kuchuk, I., Bouganim, N., Pond, G., Verma, S., Segal, R., Dent, S., Gertler, S., Song, X., Kanji, F., & Clemons, M. (2016). Can the referring surgeon enhance accrual of breast cancer patients to medical and radiation oncology trials? The ENHANCE study. *Curr Oncol*, *23*(3), e276-279. https://doi.org/10.3747/co.23.2394

Borycki, E. M., & Kushniruk, A. W. (2022). Reinventing virtual care: Bridging the healthcare system and citizen silos to create an integrated future. *Healthc Manage Forum*, *35*(3), 135-139. https://doi.org/10.1177/08404704211062575

Fahim, C., McConnell, M. M., Wright, F. C., Sonnadara, R. R., & Simunovic, M. (2020). Use of the KT-MCC strategy to improve the quality of decision making for multidisciplinary cancer conferences: a pilot study. *BMC Health Serv Res*, *20*(1), 579. https://doi.org/10.1186/s12913-020-05143-3

Kaas, R., Hart, A. A., & Rutgers, E. J. (2005). The impact of the physician on the accrual to randomized clinical trials in patients with primary operable breast cancer. *Breast*, *14*(4), 310-316. https://doi.org/10.1016/j.breast.2005.01.004

Rahman, S., Majumder, M. A., Shaban, S. F., Rahman, N., Ahmed, M., Abdulrahman, K. B., & D'Souza, U. J. (2011). Physician participation in clinical research and trials: issues and approaches. *Adv Med Educ Pract*, *2*, 85-93. https://doi.org/10.2147/AMEP.S14103

Sim, A. J., Redler, G., Peacock, J., Naso, C., Wasserman, S., McNitt, K. B., Hoffe, S. E., Johnstone, P. A. S., Harrison, L. B., & Rosenberg, S. A. (2020). Harnessing COVID-Driven Technical Innovations for Improved Multi-Disciplinary Cancer Care in the Post-COVID Era: The Virtual Patient Room. *Cancer Control*, *27*(1), 1073274820964800. https://doi.org/10.1177/1073274820964800

Spaar, A., Frey, M., Turk, A., Karrer, W., & Puhan, M. A. (2009). Recruitment barriers in a randomized controlled trial from the physicians' perspective: a postal survey. *BMC Med Res Methodol*, *9*, 14. https://doi.org/10.1186/1471-2288-9-14

Tomlinson, J., Medlinskiene, K., Cheong, V. L., Khan, S., & Fylan, B. (2019). Patient and public involvement in designing and conducting doctoral research: the whys and the hows. *Res Involv Engagem*, *5*, 23. https://doi.org/10.1186/s40900-019-0155-1

Treweek, S., Lockhart, P., Pitkethly, M., Cook, J. A., Kjeldstrom, M., Johansen, M., Taskila, T. K., Sullivan, F. M., Wilson, S., Jackson, C., Jones, R., & Mitchell, E. D. (2013). Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open*, *3*(2). https://doi.org/10.1136/bmjopen-2012-002360