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**FACULTY OF GRADUATE AND
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Laparoscopic Colorectal Surgery – Canadian Practice Patterns and the Role of the Hand Assist Device

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Laparoscopic Colorectal Surgery – Canadian Practice Patterns and the Role of the Hand Assist
Device

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4321077

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the
requirements for the MSc Degree in Epidemiology

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Your file Votre référence
ISBN: 978-0-494-66246-5
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ISBN: 978-0-494-66246-5

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ABSTRACT

Objectives: 1) To identify laparoscopic colorectal surgery practice patterns in Canada, 2) To systematically review the literature comparing hand assisted laparoscopic surgery to conventional laparoscopic surgery and 3) To design a randomized controlled trial protocol comparing conventional laparoscopic to hand assisted laparoscopic colorectal resections.

Methods: A national cross sectional study was undertaken of Canadian General Surgeons with respect to their practice patterns specific to laparoscopic colorectal surgery. A systematic review comparing Conventional laparoscopic to Hand-Assisted Laparoscopic colorectal resections. A randomized controlled trial protocol with methodological discussions regarding issues in surgical trials was written.

Results: The majority of Canadian General Surgeons are offering laparoscopic colorectal resections although the volume per surgeon appears to be low. The main barriers to adoption are operating time and lack of formal minimally invasive surgery training. There were two trials identified for inclusion in the systematic review with a total of 94 subjects with some methodological weaknesses. A potential trend towards decreased conversion to open surgery in the hand assisted group was identified. A protocol is presented for a trial comparing hand assisted to conventional laparoscopic colorectal surgery.

Conclusion: A large percentage of Canadian surgeons perform laparoscopic colorectal resections although many perform less than one case per month. The limited number of trials performed and their associated methodological weaknesses and heterogeneity does not allow a reliable assessment of the relative benefits of hand-assisted and conventional laparoscopic resections for colorectal disease. Additional adequately powered and methodologically sound trials are needed to determine if there is a clinically important difference in perioperative outcomes

Acknowledgements

Each section of this thesis has helped me appreciate important lessons that I will take into my academic career and hopefully be able to impart and share with surgical residents and surgeons. Cross-sectional studies are much more involved than I ever dreamt, with multiple steps and logistical issues. The use of multivariate regression and other statistical tests were interesting and educational to use in a 'real world' scenario. The team approach to research is also indispensable to me and I learned the value of this in this section as well as the other components of my thesis.

Knowledge of systematic reviews will be an important tool for me in the future as it will precede any consideration of performing a trial. Again, the multiple steps and time investment required to properly complete a systematic review surprised me. Completing more reviews in the future will be part of my research goals.

Finally, writing the RCT protocol and the protocol for the economic analysis will hopefully be my first step in successfully constructing well designed trials in the future that will help in the care of patients.

I would never have completed this thesis without help from a number of individuals. First, I would like to thank Sophia and Naila (my two beautiful daughters) and my wife Nimet for putting up with me and what must feel like a never ending educational process that I have undertaken; especially my wife who has supported me through residency, two fellowships and

now this Masters. I would also like to thank my Mom, Dad and sister for all the support and encouragement they have always given me and continue to give me. The Department of Surgery especially Dr. Poulin and Dr. Mamazza have been supportive of my career development and have served as great mentors for me. Without Dr. Brenda Wilson's guidance, I would likely not be in the Epidemiology program am very grateful to her and the chocolates I give her are not enough thanks. I would also like to thank all the professors within the Department of Epidemiology at the University of Ottawa for their efforts to further educate me. Also, the efforts and kindness of Fay Draper have been much appreciated and definitely enhances the program here. Finally, Dr. Grimshaw and Dr. Coyle have been fantastic thesis supervisors and I have learned a tremendous amount from them in undertaking this final portion of my Masters – I do not think I could have had better supervisors and count their involvement as a great stroke of luck for me; they are also very nice and are great examples of remaining humble in spite of great success and ability. I appreciate the time they have taken out of their schedules to help me and I look forward to their mentorship in the future.

Overall, this has been a humbling yet edifying experience which I am both happy and fortunate to have undertaken.

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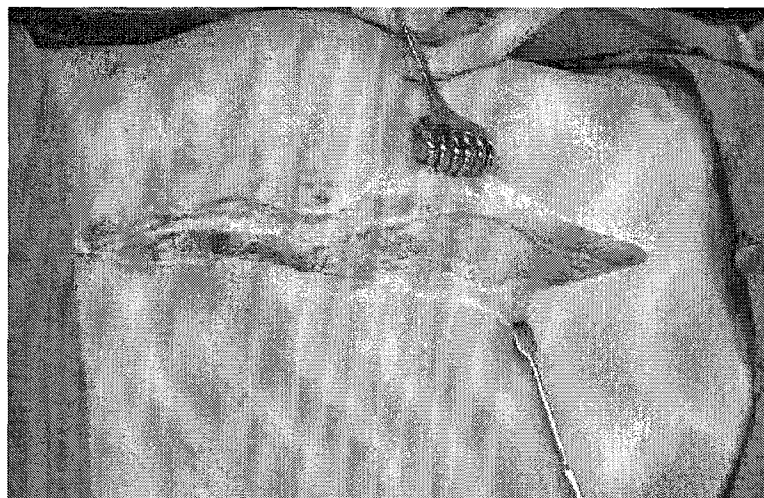
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Chapter 1 - INTRODUCTION

Colon surgery has undergone great change over the last 15 years. Prior to 1991, all colon surgery was done using one method – a laparotomy. A laparotomy involves a fairly long incision (15-30 centimeters) on a patient's abdomen – this is usually referred to as the 'open' approach (see figure 1). With the advent of laparoscopy, practice began to change.

Figure 1.1 (laparotomy incision)



Laparoscopy is a technique whereby a 5-10 millimeter diameter camera (see figure 2) is inserted into the abdominal cavity usually via a small (5-10 millimeter) incision in the umbilicus. In order to create a space to operate, carbon dioxide gas is insufflated to create a 'pneumoperitoneum'. Additional operating instruments are then inserted via 'trocars' with these trocars ranging between five to twelve millimeters in size. The image from the camera is displayed on a television screen (at the present time usually flat plasma screens) and in this way the surgeon is able to perform an operation without the need for a large incision (see Figure 3).

Figure 1.2: laparoscope

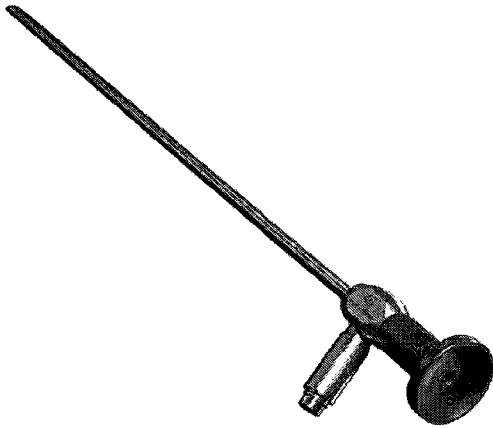
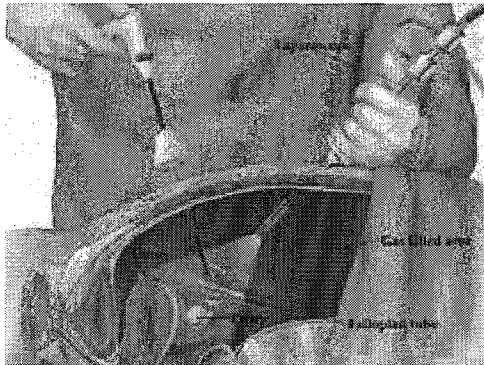


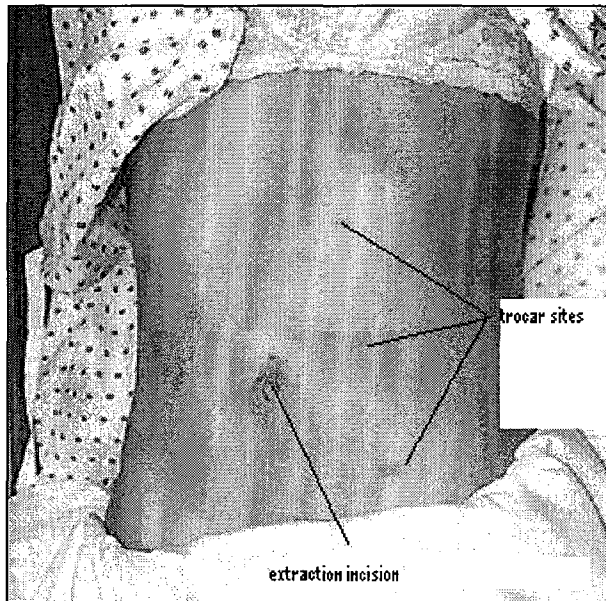
Figure 1.3: operating with the help of a laparoscope



The first operation in general surgery to be performed in this manner was removal of the gallbladder (cholecystectomy). Laparoscopic cholecystectomies were first performed in the late 1980's and quickly gained widespread dissemination throughout the entire general surgery community due to the dramatic decrease in length of stay and pain for patients^{13,14}. It did not take long for surgeons to adapt this technique to other areas in the abdominal cavity.

In 1991, the first laparoscopic colon resection was performed. Case series, prospectively collected data on cohorts, and finally large randomized control trials followed^{4,5,12}. At the present time the data from randomized control trials supports laparoscopic colon resections as an alternative to the traditional 'open' resection^{4,5}. In laparoscopic resections, dissection and ligation of vessels can be done in addition to transection of the bowel. For removal of the specimen, a small extraction incision is still required but is usually 4-5 centimeters (see Figure 4). Compared to open resections, laparoscopic resections result in a decreased length of stay of approximately one day, decreased pain for patients, quicker return of bowel function and equivalent oncologic outcomes with a minimally invasive approach^{4,5,12}.

Figure 1.4: extraction incision and trocar sites



These benefits come at a cost of increased operative time and the fact that laparoscopic colon resection is technically more difficult as tactile feedback is lost. In addition, problems such as hemorrhage which can easily be controlled in the majority of open cases with digital pressure and placement of a suture cannot be so easily dealt with in laparoscopy.

To address these obstacles, a hybrid approach has emerged – Hand Assisted Laparoscopic Surgery. A specially designed portal for the surgeon's hand to be introduced into the abdominal cavity while still maintaining a pneumoperitoneum was developed (Figure 5). Thus, the operation is still performed with the camera providing visualization in addition to other operating instruments used through placement of trocars. One issue that arises is that for placement of the hand-port, a slightly increased incision length is necessary compared to conventional laparoscopy – usually 2-3 cm more. There is less research evaluating Hand-Assisted Laparoscopic colon surgery compared to the conventional laparoscopic approach. The existing literature which consists mainly of case series with two randomized control trials (with a total of 94 patients in these trials) has not found a difference in perioperative outcomes – length of stay, return of bowel function, complication rates or quality of life. The advantages suggested by experts in the field are decreased operative time, and because of the return of tactile sensation it is an approach that many surgeons accept as easier to adopt.

Figure 1.5: Hand Assist Port



Given the increased technical difficulty, surgeons need significant additional training to become competent in laparoscopic colon surgery. This contrasts with the introduction of earlier laparoscopic operations (for example laparoscopic cholecystectomies), where surgeons would attend weekend courses and feel comfortable performing these procedures independently.

Although the learning curve for laparoscopic colon resection has not been defined, the suggested number of cases done under supervision range from 20-40⁷ – a volume that is difficult to obtain for residents and surgeons in practice. There are many courses held for practicing surgeons to attend at various centers to acquire the advanced laparoscopic skills necessary for colon resection although in Canada these are almost exclusively aimed at conventional laparoscopy. Interestingly, there are many more hand-assist courses taught in the United States although the reason for this has not been clear.

There were several objectives that were identified as part of this thesis. The first is to establish the practice patterns within Canada at the present time with regards to laparoscopic colon resections – which surgeons are offering them and are there regional variations? In addition, what are the obstacles to adoption and what are the preferred methods of skill acquisition? No study had been done in Canada previously to gather this data.

Advanced laparoscopic procedures are technically difficult and associated with a long learning curve. This may be secondary to the lack of tactile feedback. Hand-assist surgery returns this tactile sensation and it has been hypothesized that not only can the surgery become technically easier but this could also lead to decreased operative time. Are the benefits of a minimally invasive technique retained when the hand assist device is used instead of a conventional laparoscopic approach? The second objective of this thesis is to determine how hand assisted surgery compares to conventional laparoscopy and determine if, based on the current literature, there appears to be a difference in perioperative or long term outcomes. A systematic review was done to accomplish this – there was no systematic review in the literature prior to this.

The systematic review results have led to the conclusion that further randomized trial(s) would be justified and should include an economic analysis and quality of life assessment. There are many issues in the design of a surgical randomized controlled trial. The next part of the thesis consists of protocol for a proposed randomized controlled trial comparing hand assisted to conventional laparoscopic surgery. This has been written in an extended CIHR format as there are additional sections for discussion of methodological issues in surgical trials. A protocol for an economic analysis has also been done and is attached as an appendix to this protocol.

Chapter 2: Minimally Invasive Trends in Canadian Colorectal Surgery: The MISTICC Survey

2.1 Introduction

In this chapter the text of the MISTICC survey will be presented. It was undertaken to understand the current use of laparoscopy for colorectal surgery in Canada. It provides the context in which this thesis is written. To undertake research projects in minimally invasive colorectal surgery, it is helpful to know what is currently happening in Canada.

I was the lead researcher for the project and oversaw all aspects of it. I was involved with the conceptualization of the project (with Dr. Robin Boushey), responsible for the design of the questionnaire (with Dr. Boushey supported by Drs. Grimshaw and Graham), survey administration (with Ms. Haggart and Dr. Balaa), checking data entry, data analyses and logistic regression (with Ms. Haggart supported by Ms. Sabri – a biostatistician), and preparing the manuscript for publication. It was an extremely time consuming endeavor involving a broad team with a variety of steps involved.

It has been accepted for publication in the Canadian Journal of Surgery which is the most appropriate journal for publication to reach the surgeons from whom this data came from and is most directly applicable to.

2.2 *Manuscript relating to survey of general surgeons*

THE ADOPTION OF LAPAROSCOPIC COLORECTAL SURGERY: A NATIONAL SURVEY OF GENERAL SURGEONS

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Disclosures: The Minimally Invasive Surgery Research Group at the Ottawa Hospital is supported by unrestricted educational grants from Covidien Canada and Storz Canada. G. Martel is supported by a Fellowship Award in the area of knowledge translation from the Canadian Institutes of Health Research. . J. Grimshaw holds a Canada Research Chair in Health Knowledge and Transfer

Abstract

BACKGROUND: Laparoscopic surgery may become the standard of care for the treatment of colorectal disease. Little is known regarding Canadian patterns of practice, as well as limiting factors and strategies for adoption among surgeons.

METHODS: A 28-item questionnaire was sent to all general surgeon members of the Royal College of Physicians and Surgeons of Canada. Descriptive and correlative information was derived using chi-squared, Wilcoxon rank sum, t-test, and multivariate logistic regression.

RESULTS: The return rate was 55% (694/1,266). A total of 67% (462/694) [95% CI: 63%-70%] of respondents performed colorectal surgery. Of these, 54% perform laparoscopic colorectal surgery. Multivariate logistic regression identified five factors related to performing laparoscopic colorectal surgery: fewer years in practice ($p<0.0001$), male gender ($p=0.015$), practicing in the province of Quebec ($p=0.0049$), university-hospital affiliation ($p=0.034$), and minimally invasive surgery fellowship training ($p=0.023$). Lack of adequate operating time and formal training were the main reasons cited by surgeons not offering laparoscopic colon resections. Most surgeons (67%) felt that site visits from a minimally invasive surgeon would represent the most effective training method for acquiring advanced laparoscopic skills.

CONCLUSION: Approximately half of Canadian general surgeons are offering laparoscopic colorectal resections. Recent graduation, male gender, practice location, university-hospital affiliation, and minimally invasive surgery training appear to be significant predictors for offering a laparoscopic approach. Lack of operative time and formal training are the main barriers to adoption. Site visits by trained laparoscopic surgeons is the preferred method of acquiring advanced skills.

Key Words: Minimally Invasive Surgery, Cross-Sectional Study, Survey, Colorectal, Adoption, Dissemination.

Introduction

Three main methods are currently used to perform a colorectal resection: the traditional 'open' technique via a laparotomy, the laparoscopic approach, and a hybrid hand-assisted laparoscopic utilizing a mini-laparotomy incision to use a device that allows the surgeon's hand to be introduced while maintaining pneumoperitoneum. As more evidence from randomized trials demonstrating the efficacy and safety of the laparoscopic approach becomes available,¹⁻⁷ surgeons are increasingly pressured to offer minimally invasive procedures to patients with both benign and malignant colorectal pathology. Several advantages of laparoscopic colorectal surgery seem to drive patient and surgeon preference for this technique, including diminished incisional pain, a shorter period of postoperative ileus, and reduced length of hospital stay.^{8,9}

A recent survey of community general surgeons in Ontario revealed that less than 5% of respondents performed a high volume of laparoscopic colorectal procedures (>20/year).¹⁰ Surveys from the United States and the United Kingdom have reported variable adoption rates.^{11, 12} Recent publications indicate that more Canadian surgeons may be adopting this technology.¹³⁻¹⁵ Canada-wide adoption rates, regional variations, and factors determining the incorporation of laparoscopic colorectal surgery into practice have not been defined in the literature. The Minimally Invasive Surgical Trends in Canadian Colorectal Surgery survey was designed to elicit the opinions of surgeons regarding the current status of laparoscopic colorectal surgery in Canada.

Methods

A 28-item questionnaire was developed to ascertain surgeons' personal and professional characteristics, details on the types and volume of laparoscopic colorectal procedures they performed, their views on the advantages and disadvantages of laparoscopic colorectal surgery, and the most effective methods for acquisition of advanced minimally

invasive surgery (MIS) skills. A French version (n=205) was generated by Translation Services at The Ottawa Hospital and was verified by a bilingual surgeon for proper surgical terminology. The survey was piloted with eight general surgeons at The Ottawa Hospital prior to mailing. Approval was obtained from the Ottawa Hospital Research Ethics Board.

We identified all general surgeons in Canada who had a practice address registered with the Royal College of Physicians and Surgeons of Canada (RCPSC) (n=1,266). Surveys were numbered with a unique mail identification code to ensure confidentiality. A modification of Dillman's Tailored Design Method was used to maximize the response rate.¹⁶ Briefly, surgeons were mailed (i) an introductory letter about the study survey two weeks prior to the questionnaire, (ii) a package containing a reminder letter, the questionnaire and a return-stamped envelope on day 14, and (iii) two additional mailings to non-respondents on days 28 and 42. Duplicate responses were discarded based on identification codes.

Completed surveys were digitally scanned into an Excel database using the TELEform[®] software (version 10.0, Cardiff, San Diego, CA). The file was exported into SPSS[®] (version 13.0, SPSS Inc., Chicago, IL). To ensure data integrity, 100 questionnaires were randomly audited by three individuals. Extreme outliers and any other values that appeared inconsistent with the remainder of the data set were identified and verified.

Statistical analysis was performed using SPSS[®]. Pearson's χ^2 tests and t- tests were used to assess differences between groups in categorical and continuous variables. Wilcoxon rank sum tests were used to compare median estimates. Univariate and multivariate logistic regression were used to identify predictive factors for performing laparoscopic resections. A p-value of less than 0.05 was considered statistically significant. No adjustment was made for multiple testing.

Results

Demographic data of respondents (table 1).

Of the 1,266 surveys mailed, 694 (55%) were returned. Forty-two (3%) surveys were ineligible (retirement, blank form, invalid address) and were excluded from analysis, yielding a response rate of 53% (652/1,224). There were no statistically significant differences in response rates based on province, gender, or language of correspondence (data not shown).

The majority of respondents were male surgeons (85%, n=501), had affiliation with a university teaching hospital (53%, n=313), and practiced in Ontario (42%, n=249) or Quebec (20%, n=122). The age distribution of surgeons was widespread, but a majority were 40-50 years old (31%, n=189), and had been in practice for less than 10 years (37%, n=223). Most respondents performed colorectal surgery (433/652, 67%, 95% CI [63%, 70%]). These surgeons were further sub-classified into two groups: group 1 who performed laparoscopic colorectal surgery (54%, n=232), and group 2 who only performed open colorectal surgery (46%, n=211).

The province with the highest proportion of surgeons performing laparoscopic colorectal surgery was Quebec (67%), followed by British Columbia (60%), Ontario (57%), Saskatchewan (54%), Alberta (45%), Manitoba (38%), Nova Scotia (36%), New Brunswick (22%), and Newfoundland (10%).

Surgeons performing laparoscopic colorectal surgery (group 1).

Surgeons in group 1 were significantly younger (45.5 vs. 49.8 years, $p<0.002$), had fewer years in practice (14.0 vs. 17.3 years, $p<0.005$), and were more likely to practice in academic centers (60% vs. 50%, $p=0.030$) than were group 2 surgeons (table 2).

Respondents in group 1 reported a median number of 40 (interquartile range [IQR], 24-70) abdominal procedures during the previous 12 months, approximately 10 (IQR, 4-20) of which were performed laparoscopically. Almost all (95%) of group 1 surgeons considered benign colorectal conditions to be appropriate indications for performing a laparoscopic

resection. Additionally, 76% considered a laparoscopic resection of colorectal cancer with curative intent to be an appropriate indication, increasing to 79% for palliation. The most commonly performed laparoscopic colorectal resections are displayed in table 3.

Most group 1 surgeons (81%) were aware of hand-assist devices for laparoscopic colorectal procedures. However, only 6% performed hand-assisted laparoscopic colorectal procedures.

Surgeons performing open colorectal surgery (group 2).

A small percentage of surgeons (6%) indicated that a patient had refused surgery because they did not offer a laparoscopic resection. The majority (94%) was aware that hand-assist devices were being used to perform laparoscopic colorectal surgery, although 73% did not feel the use of these devices would influence their decision to undertake laparoscopic colorectal surgery. These surgeons undertook a range of laparoscopic surgery for other conditions including laparoscopic cholecystectomy (99%) and appendectomy (73%), laparoscopic ventral hernia (27%) and inguinal hernia (27%) repairs (Figure 1).

Perceived barriers and facilitators to the adoption of laparoscopic colorectal surgery.

A total of 47% of respondents in group 1 felt that surgeons are not appropriately reimbursed for laparoscopic colorectal surgery, compared to 24% in group 2 ($p < 0.0001$). Only 29% of surgeons in group 1 agreed that an increase would influence their decision to perform more laparoscopic resections. Approximately 9% of surgeons in group 2 agreed that an increase in reimbursement would influence their decision to learn to perform laparoscopic procedures.

In Group 1 (table 4), more surgeons “agreed” or “strongly agreed” that a lack of available operating time (55%) and patient factors (55%) influenced their decision to offer a laparoscopic approach compared to (i) not having adequate laparoscopic facilities at their institution (25%,

p=0.0004), (ii) already being satisfied with the number of laparoscopic colorectal procedure being performed at their institution (34%, p=0.0061), (iii) not being comfortable operating without tactile sensation (23%, p=0.0002), and (iv) awaiting further evidence from clinical trials (13%, p=0.0001).

In Group 2 (table 5), surgeons felt that a lack of formal training (51% “agreed” or “strongly agreed”) and inadequate operating time (57%) were the main reasons for not performing laparoscopic colorectal surgery compared to all other reasons (see table 5) combined (27%, p<0.0001). Importantly, surgeons in group 2 were less comfortable operating without tactile sensation compared to surgeons in group 1 (63% vs. 44%, p=0.0085).

Most respondents in group 1 (67%) and group 2 (68%) “strongly agreed” or “agreed” that a visit from a MIS-trained surgeon was their preferred method for acquiring advanced MIS skills (table 6). Fellowships were rated the lowest among the different types of training methods.

Identification of factors associated with offering laparoscopic surgery (table 7).

After univariate analysis comparing demographic factors among those offering laparoscopic surgery, variables with a p-value ≤ 0.15 were selected for multivariate analysis using stepwise logistic regression. As well, surgeon age was found to be highly correlated with years of surgical experience ($r= 0.941$, $p<0.0001$). As such, it was excluded as the number of years of experience was thought to be more clinically relevant. There was no statistical correlation between MIS training and the province of practice.

On multivariate analysis, geographical location in Quebec (OR 5.40, 95% CI [1.67, 17.48], p=0.0049), male gender (OR 2.28, 95% CI [1.18, 4.43], p=0.015), MIS subspecialty training (OR 2.12, 95% CI [1.11, 4.06], p=0.023), and university-hospital affiliation (OR 1.65, 95% CI [1.04, 2.62], p=0.034) were all found to be independent significant predictors for being a surgeon that offers laparoscopic colorectal surgery (group 1). Moreover, the number of years of surgical experience was strongly inversely predictive of offering laparoscopic colorectal surgery

(OR 0.94, 95% CI [0.92, 0.97], $p < 0.0001$). No interaction effects were detected between any of the significant factors.

Discussion

Approximately half of general surgeons performing colorectal surgery in Canada appear to offer a laparoscopic approach for both benign and malignant conditions. MIS fellowship training, male gender, having fewer years of surgical experience, university-hospital affiliation, and practicing in Quebec were factors found to be significantly predictive of performing laparoscopic colorectal surgery. Lack of formal training and inadequate operating time were the main obstacles identified by surgeons not offering this approach. A visit from a trained MIS surgeon appears to be the preferred method to acquire advanced laparoscopic skills among both groups.

Several limitations should be considered. First, even with an acceptable response rate such as ours, it is possible that proponents of MIS would be more likely to respond to a survey of this type, thus introducing a potential source of response bias. Second, the 1,266 subjects only included surgeons who had a practice address listed with the RCPSC. An additional 600 surgeons who do not have a practice address listed with the RCPSC could not be included in the study. In addition, surgeons who may have only recently entered the profession were not included in the RCPSC mailing list. With the finding of recent graduation being a predictive factor, this limitation may have underestimated the influence of recent graduation. Finally, overestimations of case volume likely occurred due to recall bias.

The strengths of the study lie in the satisfactory response rate, yielding a large sample size. This sample appears to be representative of the Canadian surgical community as there appeared to be minimal response bias, as evidenced by our comparison of demographic

factors. Our use of a multivariable statistical model strengthens our ability to identify factors predictive of offering laparoscopic colorectal surgery.

A recent survey of community general surgeons in Ontario found that fewer than 5% of respondents performed high volume of laparoscopic colorectal surgery.¹⁰ This report was limited by its focus upon community surgeons from a single province. Another cross-sectional study from the United States has demonstrated that 48% of members of the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal Endoscopic Surgeons performed laparoscopic resections for colorectal diseases.¹¹ A notable discrepancy between our study and the American survey is the difference between rates of colon cancer procedures carried out for curative reasons. Mavrantonis et al. reported that only 15% of respondents performed laparoscopic colon cancer surgery for curative purposes, while our respondents reported a much higher rate of 76%. One possible explanation for this difference could be that the U.S. study was done prior to the release of results from large prospective trials.^{3, 5, 6} These studies may have had an impact on surgical practice. The proportion obtained in the current survey is comparable to a study of the Association of Coloproctology of Great Britain and Ireland from 2005 which found that 78% of surgeons who performed laparoscopic resection did so for benign and malignant conditions.¹²

The current study is among the first to derive correlative information and limiting factors to the performance of laparoscopic colorectal procedures. One such predictor was that the younger the surgeon, the more likely a laparoscopic resection would be to be offered. It was also found that surgeons in academic centers are more likely to offer laparoscopy. Surgeons trained in recent years may be feeling more comfortable with laparoscopic colorectal resections as there is more exposure to this method as most surgical training occurs in academic centers. Many authors have argued that colonic resections are technically more challenging than other laparoscopic procedures.^{17, 18} As such, one could reason that the degree of supervision available during residency training may be principally important, particularly when compared to

the rapid adoption of laparoscopic cholecystectomy following limited training in the early 1990s.¹⁹ Nevertheless, only 18% of general surgery residents in Canada believed that their training in advanced laparoscopy in 2003 would be adequate upon graduation, and most were concerned about their ability to acquire these skills once in practice.²⁰

A fellowship in Minimally Invasive Surgery is an option for individuals interested in acquiring advanced laparoscopic skills,²¹ and it is not surprising to find that acquisition of this fellowship was a predictor for performing laparoscopic resections. The number of surgeons pursuing fellowship training may have been underestimated as a result of fewer recent graduates having a practice address with the RCPSC. The number of fellowship programs and positions has increased dramatically over the past five years, which highlights the importance of this technology to new general surgeons. Interestingly, completing a colon and rectal surgery fellowship was not a predictive factor of performing a laparoscopic resection on multivariate analysis – this may reflect the volume of laparoscopic cases done in this type of fellowship.

Provincial variations are significant in this study. Surgeons in Quebec were more likely to report undertaking laparoscopic colorectal resections when compared to other provinces and the reason for this is unclear. The provinces ranking second and third in percentage of surgeons performing laparoscopic resections were Ontario and British Columbia although these were not statistically significant findings. These along with Quebec are the three most populous provinces. The fact that a greater proportion of surgeons in these three provinces perform laparoscopic resections may be due to a greater ease of access to training facilities, as all three have numerous academic centers and community hospitals that act as training facilities. The proportion of surgeons in Atlantic Provinces (Nova Scotia, New Brunswick, and Newfoundland) performing laparoscopic colorectal resections was below the national average. It is possible that a “critical mass” of surgeons in a region is necessary before a novel procedure gains acceptance and becomes adopted. As such, less populous areas may lack this support. A follow-up survey of surgeons practicing in Eastern provinces may be useful in identifying

reasons for the lack of widespread adoption of laparoscopic colorectal surgery, as well as possible change in time.

One of the predictive factors identified for performing laparoscopic resections was male gender. The reason for this is unclear, but may be related to practice type variations or other intangible factors such as exposure to video games.²²

Operative time and lack of formal training appear to be the main barriers to offering more laparoscopic procedures or learning to perform laparoscopic colorectal surgery. Birch and colleagues have identified similar barriers in their survey of Ontario community surgeons.¹⁰ When considering the two main obstacles, operating time does not appear to be something that will increase significantly within the current health care environment in Canada. Therefore, the obstacle that can be more easily addressed concerns skill acquisition.

While fellowships in advanced laparoscopy may become increasingly valuable for junior trainees, the most commonly preferred method of skill acquisition was in fact found to be the visit of an expert MIS surgeon to the center where the surgeon practices, and the proctorship of cases within that setting. One of the keys to being able to perform a laparoscopic colon resection is having the appropriate equipment available. It is also important that operating room staff, from scrub nurse to anesthetist, be familiar with advanced laparoscopic techniques. A visit by an experienced surgeon (possibly with a nurse/anesthetist) has the potential to deal with these logistical issues. Evidence exists in the literature to suggest that targeted mentorship of advanced laparoscopy can be successful.¹³ The perceived need for visits by expert MIS surgeons raises several issues regarding the funding of such activities. In the Canadian context, we believe that such activities would be best supported by provincial ministries of health and local health networks, with the goal of standardizing the delivery of advanced surgical care within health regions.

Nevertheless, our results would suggest that even among those already offering laparoscopic colorectal surgery, laparoscopic abdominal operations account for a median of

only approximately 10 yearly procedures. This finding is troubling and raises important concerns regarding the delivery of advanced laparoscopic surgical care. Indeed, our data seem to indicate that a large proportion of general surgeons perform less than one case of laparoscopic colorectal surgery per month. Even with advanced laparoscopic surgery training, it is likely that this case-volume relationship is too small to maintain proficiency. For those surgeons who learned laparoscopy through various week-end courses, it is unlikely that this operative volume would allow ascension along the learning curve. Further work is needed to evaluate actual case volumes in Canada, as our survey did not expressly address this question. In the meantime, we believe that surgeons must make every effort to practice safe laparoscopic colorectal surgery. Surgeons should seek sufficient training to carry out advanced laparoscopic colorectal surgery, particularly in the context of malignant pathologies. Careful patient selection,²⁴ particularly in the earliest portion of the learning curve, represents another useful strategy. We further advocate careful review of one's outcomes through the use of prospective databases, as well as the entry of patients into multicenter trials.

With increased operative time for a laparoscopic resection, fewer cases can be done. In an environment where cases will be cancelled due to time constraints, financial reimbursement is an important aspect to examine. Only 8% of surgeons in the open group stated that they would consider learning how to do laparoscopic resections if financial reimbursement increased. Based on the survey results, even though the current fee schedule is not thought of as sufficient by many surgeons, it does not appear to affect the type of procedure offered to the patient.

In disseminating laparoscopic colorectal surgery, hand-assist devices are increasingly being used in the United States.²³ Advocates of hand-assisted laparoscopic surgery suggest that this technology can reduce operative time and may be more suitable for surgeons already in practice.²³ In Canada these devices have had a very low uptake. Surgeons in both groups demonstrated little interest in learning more about this technique. The reason for this finding is unclear, but may be related to limited awareness or concerns regarding the cost of these

devices in the context of a publicly-funded healthcare system. Little data exists regarding the cost of hand-assist devices, but one could speculate that Canadian general surgeons do not perceive these devices to be cost-effective.

There are still a number of unanswered questions regarding laparoscopy in colorectal surgery in Canada. One such question pertains to the most efficient method for practicing surgeons to acquire advanced laparoscopic skills. In light of the fact that not all graduating residents feel comfortable performing advanced laparoscopic procedures,²⁰ this issue may become important enough to make the hiring of laparoscopic surgeons in academic centers a priority.¹⁸

Conclusion

A large percentage of general surgeons are offering laparoscopic colorectal resections although many perform less than one case per month. Recent graduation, male gender, practice in Quebec, university-hospital affiliation, and formal MIS training appear to be significant independent predictors for offering a laparoscopic approach. Lack of operative time and formal MIS training are the main barriers to adopting this approach. Hospital visits by a trained laparoscopic surgeon was identified by both groups as the preferred method of acquiring the skills necessary to perform these procedures.

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Tables

Table 2.1. Demographic characteristics of questionnaire respondents (n=652).[†]

Characteristics	Frequency (%)
<i>Sex</i>	
Male	501 (85.2)
Female	87 (14.8)
<i>Age, years (mean ± sd)</i>	49.2 ± 11.1
<40	164 (27.2)
40-50	189 (31.3)
51-60	143 (23.7)
>60	107 (17.7)
<i>Years in practice (median, IQR)</i>	15.0, 18
<10	223 (37.0)
10-20	168 (27.9)
21-30	140 (23.3)
>30	71 (11.8)
<i>Province</i>	
Alberta	55 (9.2)
British Columbia	66 (11.0)
Manitoba	30 (5.0)
New Brunswick	19 (3.2)
Newfoundland	13 (2.2)
Nova Scotia	19 (3.2)
Ontario	249 (41.5)
Prince Edward Island	5 (0.8)
Quebec	122 (20.3)
Saskatchewan	21 (3.5)
<i>Hospital affiliation</i>	
University affiliated (with residents)	313 (53.1)
University affiliated (without residents)	49 (8.3)
Non-university affiliated (with residents)	66 (11.2)
Non-university affiliated (without residents)	161 (27.3)

[†] Where data are missing, categories do not add up to 100%.

Abbreviations – IQR: interquartile range; sd: standard deviations.

Table 2.2. Demographic characteristics of surgeons performing open versus laparoscopic colorectal surgery (n=433).[†]

Characteristics	LC group (n=232)	OC group (n=211)	p-value
Age, years (mean ± sd)	45.5 ± 8.9	49.8 ± 10.9	0.0001
Gender			0.090
Male	182 (54.5)	152 (55.5)	
Female	27 (42.9)	36 (47.1)	
Years in practice (median, IQR)	12.5 (6-21)	16.0 (7-27)	0.005
Hospital affiliation			0.55
University affiliated	129 (57.3)	96 (42.7)	
Non-university affiliated	87 (47.8)	95 (52.2)	
Region			0.0001
Central Canada	151 (60.2)	100 (39.8)	
Prairie provinces	28 (44.4)	35 (55.6)	
West coast	29 (60.4)	19 (39.6)	
Atlantic	10 (21.3)	37 (78.7)	

[†] Where data are missing, categories do not add up to 100%.

Abbreviations – IQR: interquartile range; LC: laparoscopic colectomy; OC: open colectomy; sd: standard deviations.

Table 2.3. Types of bowel procedures performed laparoscopically.

Procedures	Frequency (%)
Right hemicolectomy	201 (86.6)
Sigmoid colectomy	181 (78.0)
Left hemicolectomy	157 (67.7)
Stoma creation	150 (64.7)
Anterior resection of the rectum	113 (48.7)
Low anterior resection of the rectum	81 (34.9)
Subtotal colectomy	77 (33.2)
Abdominoperineal resection	56 (24.1)
Rectopexy	51 (22.0)

Table 2.4. Group 1 surgeons' attitudes to performing of laparoscopic colorectal surgery.*

Attitude	Strongly disagree or disagree	Neutral	Strongly agree or agree
I do not have enough operating time to always offer a laparoscopic approach	69 (30.1)	34 (14.9)	125 (54.8)
I am satisfied with the number of laparoscopic colorectal procedures being performed at my institution	97 (42.1)	55 (23.9)	78 (34.0)
I do not have adequate laparoscopic facilities at my institution	133 (59.4)	34 (15.2)	57 (25.5)
I am awaiting the results from further prospective randomized clinical trials demonstrating the effectiveness of the procedure prior to laparoscopic procedures on the setting of malignancy	163 (72.8)	32 (14.3)	29 (13.0)
Patient factors are the main determinant (i.e. body habitus, multiple previous surgeries) of whether I proceed with a laparoscopic approach	60 (26.2)	43 (18.8)	126 (55.0)
I am not comfortable operating without tactile sensation (i.e. inability to palpate tumor, blood vessels) in certain cases)	143 (62.7)	32 (14.0)	53 (23.3)

*Data given as count (percentage).

Table 2.5. Group 2 surgeons' ratings on potential barriers to performing laparoscopic colorectal surgery.*

Attitude	Strongly disagree or disagree	Neutral	Strongly agree or agree
I did not obtain enough formal training in laparoscopic surgery	51 (26.7)	42 (22.0)	98 (51.3)
There is inadequate financial reimbursement for laparoscopic colorectal resections	55 (29.0)	73 (38.4)	62 (32.6)
I do not have time to spend learning advanced laparoscopic techniques	66 (34.6)	42 (22.0)	83 (43.4)
I do not have adequate operating time to offer laparoscopic colorectal resections to my patients	46 (24.7)	34 (17.9)	109 (57.3)
I do not like to operate without tactile sensation (i.e. inability to palpate tumor, blood vessels)	83 (43.7)	59 (31.1)	48 (25.2)
I do not have adequate laparoscopic facilities at my institution	97 (51.6)	25 (13.3)	66 (35.1)
I have medico-legal concerns with laparoscopic colorectal resections	123 (64.4)	53 (27.7)	15 (7.8)
I am awaiting further evidence from prospective randomized clinical trials about its effectiveness prior to performing laparoscopic procedures in the setting of malignancy	79 (41.8)	52 (27.5)	58 (30.7)
Laparoscopic surgery does not offer any advantage over traditional open techniques	99 (51.8)	61 (31.9)	31 (16.2)

*Data given as count (percentage).

Table 2.6. Respondent ratings on their preferred methods for the acquisition of advanced MIS skills.*

Training method	Group 1			Group 2			Total median	p-value [†]
	Strongly disagree/ disagree (1, 2)	Neutral (3)	Strongly agree/ agree (4, 5)	Strongly disagree/ disagree (1, 2)	Neutral (3)	Strongly agree/ agree (4, 5)		
Weekend courses (didactic, laboratory format)	52 (24.1)	53 (24.7)	110 (51.2)	46 (25.4)	29 (16.0)	106 (58.6)	4	0.303
Week long courses (didactic and laboratory format with preceptorship or proctoring on laparoscopic bowel resections)	41 (18.8)	52 (23.9)	125 (57.3)	28 (15.1)	33 (17.7)	12 (67.2)	4	0.115
Trained MIS surgeon outreach (1-2 week visits involving facility assessments and instruction or assistance with laparoscopic cases)	24 (10.4)	50 (22.6)	147 (66.5)	23 (12.4)	37 (19.9)	126 (67.8)	4	0.378
Mini-sabbaticals/proctorship (1-6 months off practice to work as a trainee at a MIS training centre)	85 (39.0)	34 (15.6)	99 (45.4)	78 (41.7)	31 (16.6)	78 (41.7)	3	0.276
Fellowship (one year dedicated to MIS training)	118 (56.2)	30 (14.3)	62 (29.5)	121 (65.8)	26 (14.1)	37 (20.1)	2	0.023
Telementoring (purchase of equipment that would allow live broadcasting of mentor performing laparoscopic cases)	78 (36.1)	73 (33.8)	65 (30.1)	76 (41.1)	51 (27.6)	58 (31.4)	3	0.866

*Data given as count (percentage).

[†]Refers to comparison of across groups using chi-squared test.

Table 2.7. Identification of factors associated with performing laparoscopic colorectal surgery.

Variables (total n)	Univariate analysis			Multivariate analysis	
	n (%LC)	OR (95% CI)	p-value	OR (95% CI)	p-value
<i>Gender</i>					
Male (330)	183 (55.5%)	1.66 (0.96, 2.86)	0.068	2.28 (1.18, 4.43)	0.015
Female (630)*	27 (42.9%)	1.00	-	1.00	-
<i>Colorectal subspecialty training (65)</i>					
Training vs. no training	45 (69.2%)	2.09 (1.19, 3.69)	0.010	1.75 (0.87, 3.53)	0.12
<i>MIS subspecialty training (69)</i>					
Training vs. no training	49 (71.0%)	2.33 (1.33, 4.08)	0.0031	2.12 (1.11, 4.06)	0.023
<i>Province[†]</i>			0.0006		
Alberta (31)	14 (45.2%)	1.34 (0.43, 4.14)	0.61	1.36 (0.36, 5.09)	0.65
British Columbia (48)	29 (60.4%)	2.48 (0.87, 7.11)	0.091	3.39 (0.99, 11.63)	0.053
Manitoba (21)*	8 (38.1%)	1.00	-	1.00	-
New Brunswick (18)	4 (22.2%)	0.46 (0.11, 1.92)	0.29	0.60 (0.13, 2.88)	0.53
Newfoundland (10)	1 (10.0%)	0.18 (0.019, 1.71)	0.14	0.19 (0.017, 2.17)	0.18
Nova Scotia (14)	5 (35.7%)	0.90 (0.22, 3.68)	0.89	1.28 (0.26, 6.24)	0.76
Ontario (164)	93 (56.7%)	2.13 (0.84, 5.41)	0.11	2.79 (0.92, 8.46)	0.070
Quebec (87)	58 (66.7%)	3.31 (1.23, 8.87)	0.018	5.40 (1.67, 17.48)	0.0049
Saskatchewan (11)	6 (54.5%)	1.95 (0.45, 8.55)	0.38	2.77 (0.50, 15.32)	0.24
<i>Years in practice</i>			0.0025	0.94 (0.92, 0.97)	<0.0001
<i>Age, years</i>			0.0007		
<40 (129)	83 (63.9%)	3.82 (1.94, 7.54)	0.0001		
40-50 (126)	71 (55.9%)	2.73 (1.39, 5.37)	0.0035		
51-60 (100)	49 (48.5%)	2.03 (1.01, 4.09)	0.046		
>60 (53)*	17 (30.9%)	1.00	-		
<i>Hospital affiliation</i>					
University affiliated (226)	130 (57.5%)	1.39 (0.93, 2.06)	0.11	1.65 (1.04, 2.62)	0.034

Non-university affiliated (176)*	87 (49.4%)	1.00	-	1.00	-
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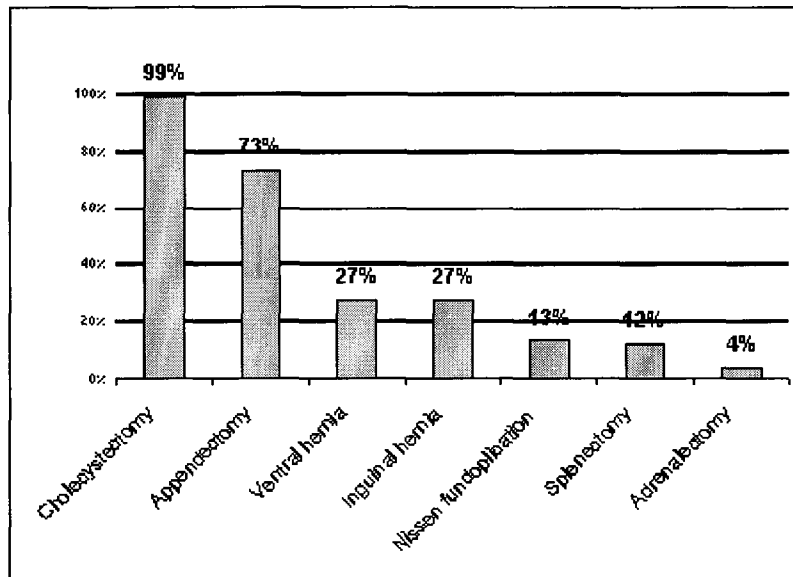
*Indicates reference group.

†Prince Edward Island (5 surgeons) and Northwest Territories (1 surgeon) excluded from logistic regression due to small numbers.

Abbreviations – LC: laparoscopic colorectal surgery; OR: odds ratio.

FIGURE LEGENDS

Figure 2.1. Percentage of group 2 surgeons (open colorectal surgeon only) performing laparoscopy, by procedure category.



2.3 Conclusion

The MISTICC survey demonstrated that there are a significant number of surgeons in Canada performing laparoscopic colon resections. Volumes remain low however at less than one abdominal laparoscopic case per month, and the main barriers to adoption of a laparoscopic technique appear to be lack of operative time and lack of formal minimally invasive surgery training.

Hand Assisted Laparoscopic surgery is suggested by many experts in the field to decrease operative time and be easier to adopt due to the return of tactile sensation. In order to understand how Hand Assist Laparoscopic surgery compares to conventional laparoscopic surgery, a systematic review was required to compare these two methods since one was not available in the literature.

2.4. Appendices

2.4.1 MISTICC Survey



3222

MLLS T.I.C.C. Surgery Survey

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SURVEY ID

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1. Do you perform surgery on the colon or rectum?
- ☐ Yes
- ☐ No If NO, please complete section C and return the survey. Thank You
2. Do you perform laparoscopic or laparoscopic assisted colorectal surgery?
- ☐ Yes If YES, please proceed to section A, question #3
- ☐ No If NO, please proceed to section B, question #15

SECTION A (To be completed only by surgeons performing laparoscopic or laparoscopic assisted colorectal procedures).

3. How many abdominal procedures did you perform between Jan 1 2004 and Dec 31 2004 for colorectal diseases (laparoscopic and non-laparoscopic)?

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4. Approximately how many of these procedures were laparoscopic or laparoscopic assisted?

--	--	--

5. In what year did you begin doing laparoscopic colorectal surgery?

--	--	--	--

6. What do you consider appropriate indications for laparoscopic colorectal resection? (Check as many boxes as appropriate)

- ☐ Benign disease eg diverticular disease, ulcerative colitis, etc
- ☐ Colorectal cancer with curative intent
- ☐ Colorectal cancer with palliative intent
- ☐ Other (Please specify):

--

7. What types of bowel resection are you performing laparoscopically? (Check as many boxes as appropriate)

- ☐ Right hemicolectomy
- ☐ Left hemicolectomy
- ☐ Anterior resection of rectum
- ☐ Low anterior resection of rectum
- ☐ Abdominoperineal resection
- ☐ Subtotal colectomy
- ☐ Sigmoid colectomy
- ☐ Rectopexy
- ☐ Stoma creation
- ☐ Other (Please specify):

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MAIL ID

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3222

For office use only
SURVEY ID

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8. For each item, circle the response that best represents your view.

	Level of Agreement				
	STONGLY DISAGREE	DISAGREE	NEUTRAL	AGREE	STONGLY AGREE
I do not have enough operating time to always offer a laparoscopic approach	1	2	3	4	5
I am satisfied with the number of laparoscopic colorectal procedures being performed at my institution annually	1	2	3	4	5
I do not have adequate laparoscopic facilities at my institution	1	2	3	4	5
I am awaiting the results from further prospective randomized clinical trials demonstrating the effectiveness of the procedure prior to performing laparoscopic procedures in the setting of malignancy	1	2	3	4	5
Patient factors are the main determinant (ie body habitus, multiple previous surgeries) of whether I proceed with a laparoscopic approach	1	2	3	4	5
I am not comfortable operating without tactile sensation (ie inability to palpate tumor, blood vessels) in certain cases	1	2	3	4	5
Other (please specify): 	1	2	3	4	5

9. Are you performing any hand-assisted laparoscopic colon procedures?

☐ Yes -->Please proceed Q12 ☐ No

10. Are you aware that hand-assist devices are being used to perform laparoscopic colon surgery?

☐ Yes ☐ No

11. Would the use of a hand-assist device which restores tactile sensation, influence your decision to perform more laparoscopic assisted colon surgery?

☐ Yes ☐ No



3222

For office use only

SURVEY ID

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12. Are surgeons appropriately reimbursed for performing laparoscopic colorectal resections?

☐ Yes☐ No-->

If No, how much of an increase in financial reimbursement would you consider to be appropriate-->

☐ 10%☐ 20%☐ 30%☐ 40%☐ 50%☐ >50%

13. If the financial reimbursement for laparoscopic colorectal procedures was to increase in Canada, would you be performing more of your colorectal procedures laparoscopically?

☐ Yes☐ No

14. Which of the following would be your preferred method for the acquisition of advanced MIS skills?

	Level of Agreement				
	STRONGLY DISAGREE	DISAGREE	NEUTRAL	AGREE	STRONGLY AGREE
Weekend Courses (didactic, dry/wet lab format)	1	2	3	4	5
Week Long Courses (this would involve didactic and lab work with a preceptorship or proctoring on laparoscopic bowel resections over a one week period)	1	2	3	4	5
Trained MIS surgeon visiting your institution for 1-2 weeks. Would involve assessment of your facilities in addition to assisting/instructing with laparoscopic cases	1	2	3	4	5
Mini-Sabbaticals/Proctorships (this would involve taking one to six months off from your practice to work at a center as a trainee in minimally invasive surgery)	1	2	3	4	5
Fellowship (one year of dedicated minimally invasive surgery training)	1	2	3	4	5
Telementoring (would involve the purchase of equipment that would make this possible and partnering with a minimally invasive surgeon who would be able to offer this type of mentoring)	1	2	3	4	5
Other (please specify): 	1	2	3	4	5

END of Section A, please skip section B and proceed to section C question 23



3222

SECTION B (To be completed by surgeons NOT performing laparoscopic or laparoscopic assisted colorectal procedures)

For office use only
SURVEY ID

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15. Have you ever had a patient refuse surgery because you do not offer a specific laparoscopic colorectal procedure in your practice?

☐ Yes ☐ No

16. Do you perform any laparoscopic surgical procedures?

☐ Yes ☐ No

If Yes, Please Specify:
(Check as many boxes
as appropriate) →

- | | |
|--|--|
| ☐ Cholecystectomy | ☐ Appendectomy |
| ☐ Splenectomy | ☐ Adrenalectomy |
| ☐ Nissen Fundoplication | ☐ Ventral Herniorraphy |
| ☐ Inguinal Herniorraphy | ☐ Other (Please specify): |

--

17. For each item, circle the response that best represents your view.

	Level of Agreement				
	STONGLY DISAGREE	DISAGREE	NEUTRAL	AGREE	STONGLY AGREE
I did not obtain enough formal training in laparoscopic surgery	1	2	3	4	5
There is inadequate financial reimbursement for laparoscopic colorectal resections	1	2	3	4	5
I do not have time to spend learning advanced laparoscopic techniques	1	2	3	4	5
I do not have adequate operating time to offer laparoscopic colorectal resections to my patients	1	2	3	4	5
I do not like to operate without tactile sensation (ie inability to palpate tumor, blood vessels)	1	2	3	4	5
I do not have adequate laparoscopic facilities at my institution	1	2	3	4	5
I have medico-legal concerns with laparoscopic colorectal resections	1	2	3	4	5
I am awaiting further evidence from prospective randomized clinical trials about its effectiveness prior to performing laparoscopic procedures in the setting of malignancy	1	2	3	4	5
Laparoscopic surgery does not offer any advantage over traditional open techniques/procedures	1	2	3	4	5
Other (please specify):					
	1	2	3	4	5



3222

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SURVEY ID

18. Are you aware that hand-assist devices are being used to perform laparoscopic colon surgery?

☐ Yes ☐ No

19. Would the use of a hand-assist device which restores tactile sensation influence your decision to perform laparoscopic assisted colon surgery?

☐ Yes ☐ No

20. Are surgeons appropriately reimbursed for performing laparoscopic colorectal resections?

☐ Yes

☐ No

If NO, how much of an increase in financial reimbursement would you consider to be appropriate:

☐ 10% ☐ 20% ☐ 30% ☐ 40% ☐ 50% ☐ >50%

21. If the financial reimbursement for laparoscopic colorectal procedures increased compared with traditional open techniques, how much would this influence your decision to learn how to perform laparoscopic colorectal procedures? (Circle one number)

1
Not at all

2

3
Somewhat

4

5
A great deal

22. Which of the following would be your preferred method for the acquisition of advanced MIS skills?

	Level of Agreement				
	STONGLY DISAGREE	DISAGREE	NEUTRAL	AGREE	STONGLY AGREE
Weekend Courses (didactic, dry/wet lab format)	1	2	3	4	5
Week Long Courses (this would involve didactic and lab work with a preceptorship or proctoring on laparoscopic bowel resections over a one week period)	1	2	3	4	5
Trained MIS surgeon visiting your institution for 1-2 weeks. Would involve assessment of your facilities in addition to assisting/instructing with laparoscopic cases	1	2	3	4	5
Mini-Sabbaticals/Proctorships (this would involve taking one to six months off from your practice to work at a center as a trainee in minimally invasive surgery)	1	2	3	4	5
Fellowship (one year of dedicated minimally invasive surgery training)	1	2	3	4	5
Telementoring (would involve the purchase of equipment that would make this possible and partnering with a minimally invasive surgeon who would be able to offer this type of mentoring)	1	2	3	4	5
Other (please specify): 	1	2	3	4	5

END Section B - please proceed to section C question #23



Section C

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SURVEY ID

--	--	--	--

23. Age:

--	--	--

24. Gender: ☐ Male ☐ Female

25. How many years have you been practicing as a surgeon?

--	--

26. In which province are you currently practicing?

- | | |
|--|---|
| ☐ Alberta | ☐ Nova Scotia |
| ☐ British Columbia | ☐ Ontario |
| ☐ Manitoba | ☐ Prince Edward Island |
| ☐ New Brunswick | ☐ Quebec |
| ☐ Newfoundland | ☐ Saskatchewan |
| ☐ Northwest Territories | ☐ Yukon |

27. How would you describe your hospital affiliation?

- ☐ University affiliated - with surgical residents
☐ University affiliated - with no surgical residents
☐ Non-University affiliated - with surgical residents
☐ Non-University affiliated - with no surgical residents

28. Do you have any formal training in the following surgical subspecialties?

- ☐ Colorectal Surgery
☐ Minimally Invasive Surgery
☐ Surgical Oncology
☐ Hepatobiliary
☐ Trauma
☐ Vascular
☐ Thoracic
☐ Other

--

THANK YOU FOR COMPLETING THE SURVEY!

Please send survey back in self addressed envelope provided.

Note: Please do not fold.

2.4.2: Introduction Letter

M.I.S.T.I.C.C.

Minimally Invasive Surgical Trends In Canadian Colorectal surgery SURVEY

Dear Colleague;

We would like to take this opportunity to introduce you to a national project that is currently being conducted by the Departments of Clinical Epidemiology and Surgery, at the University of Ottawa. As you are aware, the surgical approach to diseases of the colon and rectum has been changing dramatically with the advent of minimally invasive surgical techniques. In the next few weeks, you will be receiving a short survey that will assess your opinion with regards to the current status of laparoscopic colorectal surgery across Canada. This national project is aimed at elucidating the opinions of practicing Canadian Surgeons. The data will help us identify differences in practice patterns around the country, and more importantly, to better appreciate factors limiting the widespread application of laparoscopic colorectal surgical techniques. Ultimately, this data will assist us in generating new strategies for teaching and disseminating minimally invasive surgery across Canada. We thank you in advance for your time, and for being involved in this collaborative effort.

If you have any questions or concerns, please do not hesitate to call 613-798-5555 Xt 74761.

Sincerely,

Minimally Invasive Surgery Group – University of Ottawa

2.4.3: Reminder Letter sent to surgeons on 1st mailing (also on 2nd and 3rd mailings if needed)

M.I.S.T.I.C.C.

Minimally Invasive Surgical Trends In Canadian Colorectal surgery SURVEY

Dear Colleague;

A few weeks ago you received a letter informing you about a survey we are conducting. As we mentioned, this study will assess your opinion with regards to the current status of laparoscopic colorectal surgery. The aim is to elucidate the opinions of practicing Canadian Surgeons. The data collected will help us identify differences in practice patterns around the country, and more importantly, will help us better appreciate factors limiting the widespread application of laparoscopic colorectal surgical techniques. Ultimately, this data will assist us in generating new strategies for teaching and disseminating minimally invasive surgery across Canada. Participation in this project is strictly voluntary. All data collected will be stored in a secure data base, and we will ensure anonymity at all times. The completed survey can be returned in the self addressed and pre-stamped envelope provided. We thank you in advance for your time, and for being involved in this collaborative effort.

If you have any questions or concerns, please do not hesitate to call 613-798-5555 Xr 74761.

Sincerely,

Minimally Invasive Surgery Group – University of Ottawa

Chapter 3. Systematic Review: Hand Assisted vs. Conventional laparoscopic colorectal surgery

3.1 Introduction

The MISTICC survey revealed that a significant percentage of surgeons are performing laparoscopic colorectal resections however the volumes are fairly low. The major barriers to adoption that were identified were operating time and lack of training in advanced laparoscopic techniques. Hand assist laparoscopic surgery is a method that returns tactile feedback during laparoscopy and has been offered as a method that potentially decreases the learning curve for surgeons in undertaking minimally invasive approaches to colon surgery. The other advantage that has been suggested by surgeons who use the hand assist method is decreased operative time. Examining the literature regarding hand assist and how it compares to conventional laparoscopy therefore appeared to be one of the logical research avenues to explore; to do this a systematic review of the literature was done. The review has been undertaken using the methods of The Cochrane Collaboration.

The systematic review was by necessity a team effort. I was responsible for all aspects of the review. I was involved with every step of the review from registering the title with The Cochrane Collaboration to retrieving the articles from the library to sending emails to the authors of the included trials.

I designed the protocol with input from my co-authors. I screened the titles and abstracts. I was also involved with the data abstraction and performed the analysis on RevMan.

The review was written by me with contribution from my co-authors. The protocol has been published by The Cochrane Collaboration and the review accepted with minor revisions to be made.

3.2 Cochrane review of hand assisted versus conventional laparoscopic colorectal surgery

Hand Assisted vs Conventional Laparoscopic Colorectal Surgery

H Moloo, F Hagggar, B Hutton, J Grimshaw, D Coyle, J Mamazza, E Poulin, R Boushey

Abstract

Background

Laparoscopic surgery for colon disease has been shown to have advantages over the open approach in the perioperative period in terms of shorter hospital stay, decreased analgesic use and a more rapid return of bowel function but provides these benefits at the expense of increased technical difficulty and operative time. Hand assisted surgery is a hybrid of open surgery and laparoscopic surgery. Advocates of hand assisted laparoscopic colorectal surgery suggest that it is a method of offering patients the perioperative advantages of minimally invasive surgery without the technical difficulty and increased operative time associated with the conventional laparoscopic approach. However, thus far, this approach to colorectal surgery has not been shown to significantly improve outcomes in this patient population.

Objectives

To estimate the perioperative outcomes of hand assisted laparoscopic surgery compared to conventional laparoscopic surgery in adult patients requiring colorectal resections.

Search strategy

An electronic search strategy was developed and applied to EMBASE (1980-Aug 2007), Medline (1966-Aug 2007) and the Cochrane Register of Controlled Trials (Aug 2007). Hand searching of included studies, as well as relevant review articles and conference abstracts was also performed.

Selection criteria

Studies included randomized controlled trials (RCTs) in which adult patients were allocated to either receive hand-assisted laparoscopic surgery or conventional laparoscopic colorectal resection for benign or malignant colorectal disease. Studies were not restricted by language of publication.

Data collection & analysis

Reports of potentially relevant articles were retrieved in full text, and two reviewers independently assessed the eligibility of these studies. Data abstraction was performed independently by two reviewers. Meta-analysis of study-level perioperative outcome measures was carried out using a random effects model for weighted mean differences for continuous variables and odds ratios for dichotomous variables.

Main results

Only two randomized controlled studies met the inclusion criteria for this review (n=94). These studies were clinically heterogeneous in terms of indication for surgery; one study focused on malignant pathology and the other almost exclusively benign pathology.

Patient characteristics also varied between studies in terms of age. Meta-analysis of study-level data revealed no statistically significant difference in operative time, complication rates or conversion rates when comparing hand assisted surgery to conventional laparoscopy. Both studies were associated with methodological limitations relating to small sample sizes and allocation/concealment.

Reviewers' conclusions

The limited number of trials performed and their associated methodological weaknesses and heterogeneity does not allow a reliable assessment of the relative benefits of hand-assisted and conventional laparoscopic resections for colorectal disease. Additional adequately powered and methodologically sound trials are needed to determine if there is a clinically important difference in perioperative outcomes. Due to significant costs associated with the use of hand-assist devices, economic analyses are also warranted.

Plain Language Summary

In the past open surgery was the only method for resection of the colon or rectum. With the advent of laparoscopy, surgeons began to use a minimally invasive approach with the largest incision being an extraction site where the piece of colon or rectum could be removed. Laparoscopy is difficult to learn and also takes longer than open surgery. A new technique which is a hybrid of the two called 'hand-assisted laparoscopic surgery' uses a special device where the surgeon can use one hand to help with the surgery thus returning tactile sensation. The size of the largest incision is only a little bigger than the 'extraction' incision used in the conventional laparoscopic approach. This device is

expensive but is thought to give patients the same advantages that they get with the conventional laparoscopic approach compared to open surgery such as decreased length of stay, less pain and quicker return of bowel function. This review found that there are two trials that have compared these methods and both have a small number of patients. There is a need for larger trials that explain the manner in which the trials were conducted. An economic analysis is also needed since the hand assist device is expensive and longer follow up of patients is needed.

Background

Since the first laparoscopic cholecystectomy was performed, the technology has rapidly infiltrated different aspects of general surgery. The first laparoscopic colon resection was performed in 1991¹⁻³, but has not received widespread adoption in the surgical community. This is likely due to a variety of factors such as inadequate access to sufficient training, increased complexity and technical difficulty of the surgery, and issues surrounding colorectal cancer outcomes. The cancer-related concerns related to performing a proper oncologic resection and uncertainty about long-term survival. Several randomized control trials⁴⁻⁶ have addressed these issues demonstrating that laparoscopic surgery results in shorter hospital stay, decreased analgesic use and a more rapid return of bowel function, though a significantly longer operating time has also been documented⁴⁻⁹. Oncologic outcomes have also been found to be equivalent. A systematic review supporting the perioperative benefits with minimally invasive colorectal surgery has been published as well as a systematic review demonstrating oncologic equivalence when comparing the open and laparoscopic approaches^{8,10}.

One of the main barriers to the widespread adoption of laparoscopic colorectal resections is the perceived technical difficulty of the technique. Hand Assisted Laparoscopic Surgery (HALS) has been developed as a hybrid procedure whereby one hand can be introduced by the surgeon into the abdomen while still maintaining a pneumoperitoneum. As a result, tactile sensation is returned without the need for the laparotomy incision associated with the traditional 'open' approach. In addition to the return of tactile function, HALS offers (1) an opportunity to deal with any hemorrhage manually; (2) a potentially shorter operating time compared to conventional laparoscopic surgery¹¹⁻¹⁴ and (3) a plausibly simpler technique to adopt for surgeons who do not have the opportunity to leave their practice to learn laparoscopic colon surgery.

Description of the Condition:

Benign and malignant colorectal conditions requiring surgery. These conditions include cancer, diverticular disease, Crohns, and Ulcerative Colitis

Description of the Intervention:

This systematic review compares Hand Assisted Laparoscopic colorectal resections to Conventional laparoscopic resections.

How the intervention might work:

It is anticipated that hand assisted surgery may have decreased operative time and conversion rate compared to conventional laparoscopy while preserving the perioperative outcomes associated with conventional laparoscopy.

Why it is important to do this review:

Colorectal conditions (both benign and malignant) are common. There has been an increase in the use of minimally invasive approaches to patients with colorectal diseases. Hand-assisted surgery is a new technique of potentially offering the advantages of a minimally invasive approach. There has been no systematic review examining this issue and the findings of a review could potentially impact practice and affect the way in which a large number of individuals are treated.

Objectives

The aim of this systematic review and meta-analysis is to estimate the effects of HALS compared with conventional laparoscopy on perioperative outcomes in colorectal surgery.

Methods

Criteria for considering studies for this review

Types of studies

Randomized trials (published and unpublished).

Types of participants

Adult patients undergoing conventional laparoscopic or hand assisted laparoscopic colorectal resections for benign or malignant colorectal disease

Types of intervention

Conventional laparoscopic colorectal resection:

Surgical Treatment in which intraperitoneal gas insufflation or mechanical abdominal wall lift was used. The mobilization of the diseased bowel segment and/or dissection of the mesentery and vessels was performed utilizing a laparoscope for visualization. The anastomosis was not required to be performed intracorporeally, and division of mesentery could have been done extracorporeally using an 'extraction' incision. No 'hand-assist' devices were used.

Hand-assisted colorectal resection:

Surgical Treatment in which intraperitoneal gas insufflation or mechanical abdominal wall lift was used. A 'hand-assist' device was used to perform the dissection and/or mobilization of the colon. Studies were required to report on one or more a priori identified outcomes of interest in either the operative or post-operative period.

Chemoradiotherapy is acceptable as long as common to both treatment arms.

Types of outcome measures

Studies were required to report on one or more a priori identified outcomes of interest in either the operative or post-operative period

Primary outcomes:

Operative outcomes: duration of surgery and conversion rate

Postoperative outcomes: length of hospital stay (including re-admission within 30 days), post operative complications. We considered the following major and minor complications: (1) major complications: anastamotic leak, cardiac complications, DVT, need for reoperation, hemorrhage requiring transfusion of blood products and (2) minor complications: wound infection, urinary tract infection, ileus, minor hemorrhage.

Secondary outcomes:

Operative outcomes: reasons for conversion, frequency of intraoperative complications, blood loss, total length of incision(s), percentage of complete resection, number of lymph nodes in specimen, and margins (percentage positive and length of negative margin).

Postoperative outcomes: days to regular diet (DAT), days to resolution of ileus, days to return to normal function. Pain perception, quality of life, mortality, and 5 year survival were also sought.

Search Methods for Identification of Studies

Electronic Searches

To identify studies for inclusion in this review, detailed search strategies was developed for each of the following electronic databases:

- Cochrane Colorectal Cancer Specialised Register (Aug 2007)
- MEDLINE (1966 to Aug 2007)

- EMBASE (1980 to Aug 2007)
- CINAHL (1982 to Aug 2007)
- Cochrane Central Register of Controlled Trials (CENTRAL) (August 2007 issue)
- PsycINFO (1806 to Aug 2007)
- Social Science Citation Index (1981 to Aug 2007)
- AMED (Allied & Complementary Medicine) (1985 to Aug 2007)
- National Research Register (August issue)

Search terms

The search used a combination of controlled vocabulary and free text terms in addition to the Cochrane highly sensitive search strategy for identifying reports of randomized controlled trials (Cochrane Handbook for Systematic Reviews V 5.0). The search strategy was developed for Medline and has been revised appropriately for each database. The following search terms for Medline were adopted for each database:

1. hand assisted laparoscopic surgery
2. HALS
3. conventional laparoscopic
4. laparoscopic surgery
5. colorectal disease
6. colorectal surgery
7. colon surgery
8. rectal surgery

9. colorectal resection

Searching Other Resources:

The reference lists of all studies were checked for further potentially relevant studies.

Authors of significant papers were contacted to find other potentially relevant studies.

The following online registers of ongoing trials were searched: <http://controlled-trials.com> and <http://clinicaltrials.gov>

No language restriction was placed on searches.

Data Collection and Analysis:

We undertook a meta-analysis using a random effects models and summary odds ratio for dichotomous and weighted mean difference for continuous variables using RevMan 5.

There are two main models utilized when summarizing evidence in a systematic review: a fixed effects or a random effects model. The underlying assumption in the fixed effects model is that there is one 'true' answer that exists for the question being asked. The random effects model assumes that there may be multiple answers for an effect and that the reason for this is because of the variability that exists between studies as well as the influence of chance or random variability. Philosophically, the random effects model is the model that was subscribed to when performing the analysis. It was also used because of the possible clinical heterogeneity that could exist between the studies.

The weighted mean difference is an outcome used to summarize data that is continuous and that has used the same scale – i.e. in this review operative time in minutes. The summary odds ratio is used to describe pooled data and is the odds that an outcome occurs in an experimental group (in this analysis the hand assisted laparoscopy group) compared to the control group (conventional laparoscopy).

Selection of Studies

Two reviewers independently assessed the title and abstracts of all reports identified by electronic and manual searches. Any differences were resolved through discussion. Abstract publications were only selected when a full manuscript was obtained from the study authors.

Data Extraction and Management:

Two reviewers independently extracted the data for the primary and secondary outcomes and entered the data into paper a standardised data collection form developed for this purpose.

The data abstraction form included the following categories: (1) *Study characteristics* (place of publication, date of publication, population characteristics (diagnosis, sex, age, BMI, comorbidities), setting, detailed nature of intervention, detailed nature of comparator, detailed nature of outcomes; (2) *Results of included studies* (specifically, details of the main observed outcomes of interest. Reasons as to why an included study

did not contribute data on a particular outcome were carefully recorded to assess the possibility of selective reporting.

Discrepancies were resolved by discussion. Authors of included studies were contacted for missing data. One reviewer entered all data into RevMan 5. The second reviewer independently re-entered the data, using the double data-entry facility in order to verify the data entered

Assessment of Risk of bias in included Studies:

Two reviewers independently assessed the included studies for sources of systematic bias in trials, according to the guidelines in section 6 of the Cochrane Handbook for Systematic Reviews of Interventions 5 – the risk of bias table as described in the handbook was used. The studies were evaluated for the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Other potential quality issues were also examined and assessed (Table 3.2). Differences between the two reviewers were resolved by discussion. One reviewer transcribed this data into the Review Manager 5 (Cochrane Collaboration) and another reviewer verified all data entry for accuracy.

Measurement of Treatment Effect

Data analysis followed the guidelines outlined in Section 8 of the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5.

Dichotomous outcomes (e.g., presence/absence of complications) were reported as proportions and were directly compared (difference in proportions). We used these proportions to calculate odds ratios (ORs) and absolute risk reductions (risk differences) with 95% confidence intervals (CIs).

For continuous data (e.g., operating time, length of hospital stay) results are presented as weighted mean differences (WMD).

Review Manager 5 software (RevMan 5, Cochrane software) was used for generating the figures and statistical analyses.

Assessment of Heterogeneity:

Since two studies were identified, a statistical test for heterogeneity was not done. The heterogeneity in terms of clinical criteria (i.e. benign vs. malignant diagnosis) is described in Table 3.3.

Data Synthesis:

The results were expressed as odds ratios (ORs) and 95% confidence intervals (CI) for dichotomous outcomes and weighted mean difference (WMD) and 95% CI for continuous outcomes. We summarized the information available. A qualitative description was provided for adverse effects when this was available. For most comparisons it was not possible to carry out a quantitative analysis because of the multiple sources of heterogeneity between the included studies. A qualitative review and synthesis of these outcomes was performed.

Sensitivity Analysis:

If a sufficient number of relevant studies had been retrieved the authors had intended to conduct sensitivity analyses to assess the robustness of the review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment and unclear or inadequate blinding

Results

Results of the Search:

The search resulted in 54 hits. After initial screening and de-duplication, the full texts of 31 studies were retrieved for further assessment.

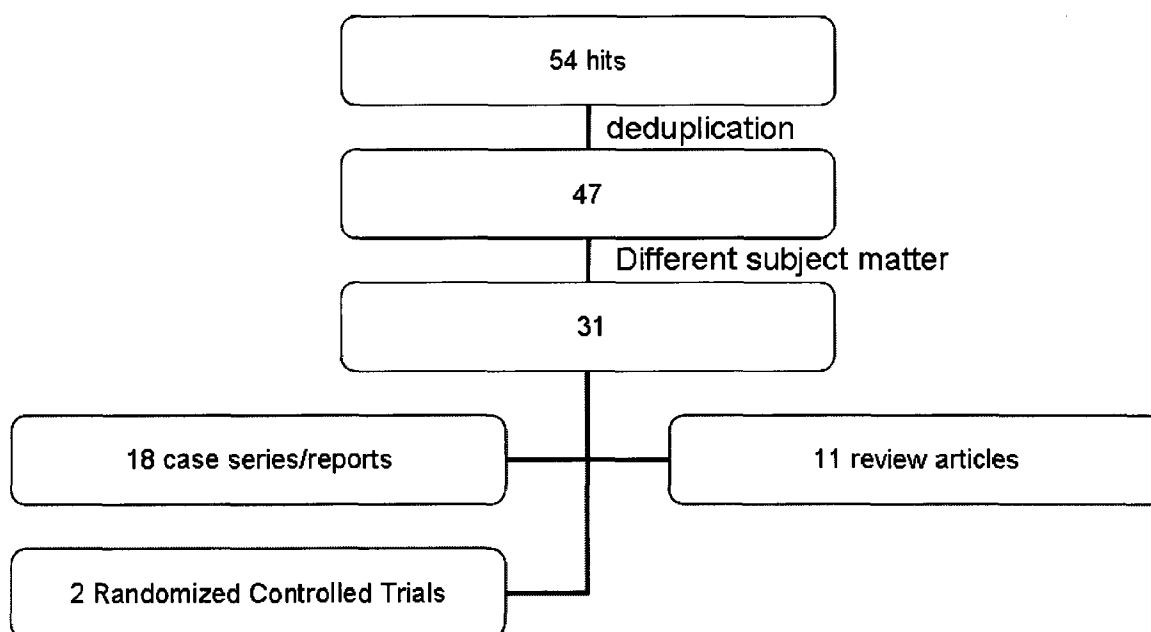
Included Studies:

Two trials (HALS study group¹⁵; Targarona et al¹⁶) met our inclusion criteria (see 'Characteristics of included studies' table for further details) with a total enrolment of 94 patients.

The HALS group¹⁵ reported their results from the planned interim analysis, but there has been no further publication since these interim findings were published

Excluded Studies:

From the search we retrieved 54 abstracts. During this process of study selection there were seven duplicates. Abstracts of the remaining 47 were reviewed: 16 were excluded due to different subject matter. For the remaining 31 abstracts, the full article was retrieved and reviewed further. Of the 31 articles that were reviewed, 18 were case series/case reports and 11 were reviews/description of the technique. There were two articles that met the prespecified inclusion criteria after completion of screening.



Description of Studies:

See: Characteristics of included studies; Characteristics of excluded studies.

The HALS study¹⁵ was multi-centered and had eight sites in three different continents, while the Targarona¹⁶ study reported results from one center. Both trials were conducted

in academic centers. The HALS study¹⁵ was industry sponsored. No trial registration number was reported in either publication. Both studies utilised the Handport for the hand assisted procedure, and the Targarona¹⁶ study also used the Omniport (a different type of hand assist device but following the same principle as the Handport).

Both studies were relatively small. The HALS group¹⁵ included 22 patients in the hand-assisted group and 18 patients in the laparoscopic group whereas the Targarona et al study¹⁶ randomized 27 subjects to each group. One study¹⁶ reported a sample size calculation based on a difference in operating time observed with surgery on the spleen. This may not have been the ideal choice since it is a solid organ that arguably may not give the minimally important difference necessary for calculating sample size. The HALS group¹⁵ reported their results from the planned interim analysis, but there has been no further publication since these interim findings were published.

The HALS trial¹⁵ excluded patients with curable colorectal cancer, whereas the Targarona¹⁶ trial included all types; as such, all patients in the HALS group trial¹⁵ had operation for benign pathology, with the exception of two patients in the conventional laparoscopy who had incurable disease.

The HALS group study¹⁵ did not identify a primary outcome, while the Targarona study¹⁶ identified duration of surgery as its primary outcome. Outcomes reported in the HALS group study¹⁵ included operating time, incision length, conversion rate, return of bowel function, length of stay, postoperative pain, and postoperative complications; outcomes

reported in the Targarona study¹⁶ included operative time, conversion rate, recovery of bowel sounds, re-feeding time, postoperative pain, postoperative complication rates, inflammatory response (measuring interleukin-6 and C-reactive protein), intraoperative cytology, lymph node retrieval, and relative costs of the procedure.

The populations of patients randomized varied between the two studies. The HALS trial¹⁵ excluded patients with curable colorectal cancer which led to a difference in the type of pathology in each group. All patients in the HALS group trial had benign pathology with the exception of two patients in the conventional laparoscopy that had incurable disease. In contrast, the Targarona trial¹⁶ had 44/54 (22 in each group) subjects being operated on for malignant pathology. Consequently, the mean age reported in the Targarona trial¹⁶ appears to be higher for both groups: 67 years vs 54 years in the conventional group and 70 years vs. 53 years in the hand-assisted group. The procedures done in the two studies were similar, although there were 7/40 cases in the HALS group trial¹⁵ involving the rectum (2 resection rectopexy in conventional group, 2 resection rectopexy in hand-assisted group, 1 low anterior resection in the conventional group, 1 low anterior resection in the hand assisted group and 1 APR in the conventional group).

Risk of Bias in Included Studies:

Results of the quality assessment are given in the Tables 3.1 and 3.2. In general, the quality of the studies assessed was fair with regard to methodology but neither was large enough to detect useful clinical differences between groups.

Table 3.1 Revised Cochrane Risk of Bias Assessment

Characteristic	HALS Group	Targarona et al
Sequence Generation	Yes	No
Allocation Concealment	No	Yes*
Blinding	No	No
Incomplete outcome data	No	Yes
Selective Outcome Reporting	No	Yes
Other sources of Bias (see table 3.2)		

*based on email correspondence with one of co-authors; not explicit in paper

Table 3.2 Other Potential Sources of Bias

Characteristic	HALS Group	Targarona et al
Sample Size Estimation	NOT REPORTED	ADEQUATE
Time of Randomization	PRE OPERATIVE – timing unclear	NOT REPORTED
Method of Randomization	Computer Generated	Concealed Envelope
Treatment Schedule Concealment	NOT REPORTED	NOT REPORTED
Blinding of Participant to Treatment	NOT REPORTED	NOT REPORTED
Blinding of Assessor immediate post operative period	NOT REPORTED	NOT REPORTED
Main Study Outcome	NOT REPORTED	Operative Time
Inclusion/Exclusion Criteria	ADEQUATE	ADEQUATE

Sequence Generation:

The HALS trial specified that patients were randomized with the use of a ‘computer’. It was not specified whether this involved generation of a random number, etc. The Targarona trial did not specify the method of sequence generation.

Allocation:

Allocation concealment was not reported in the publications of both trials. Allocation concealment was verified by e-mail correspondence with one of the authors of the study of Targarona. Incomplete information about the randomization procedure and allocation concealment was available from the HALS study.

Blinding:

Blinding with respect to participant, assessor, or statisticians was not described or reported in either paper.

Incomplete Outcome data:

The HALS paper¹⁵ was presented as an interim analysis of the first 40 patients in a planned 70 patient study. There has been no further publication found with regards to this.

Selective Reporting:

The HALS group study¹⁵ did not identify a primary outcome. Selective reporting may have occurred but the only way to ascertain this would be to examine the trial protocol. As this was a planned interim analysis, perhaps they wanted to present data on all the covariates being examined. The Targarona¹⁶ study used operative time as the primary outcome and did report on this as well as other outcomes they had identified in their methods section. To fully determine whether selective outcome reporting occurred in this study, the trial protocol would need to be available. Alternatively, if the trials had been registered, the primary outcome that was being sought would have been available and helped confirm whether there were irregularities present in the outcomes published.

Other Sources of Bias:

One main issue is that neither of the studies presented a flow diagram with the number of patients that were assessed for eligibility and then excluded or included. The reader has no idea of which patients were approached/selected to enter the trial – if the investigators were selective then this could lead to decreased external validity of the results presented. There is no information on whether patients were excluded because they did not receive the intended treatment – more detail regarding this gives the reader an indication of possible selection bias occurring.

There is no indication of when surgeons found out about the allocation of patients. If this occurred weeks in advance of the operation it is possible that selection bias could have been introduced – potentially those patients who could have been difficult to use a minimally invasive approach in could have been excluded and there is no information presented regarding post randomization exclusions to identify if this potential bias could have been introduced. Again, without a flow diagram of patients it is difficult to know whether exclusions occurred after allocation.

Further details regarding the trial team in terms of whether a research nurse was involved when speaking to patients about the trial and interventions and obtaining consent were not given. Again, if the investigators were the individuals involved in recruiting patients to the study then there is another opportunity for selection bias to occur.

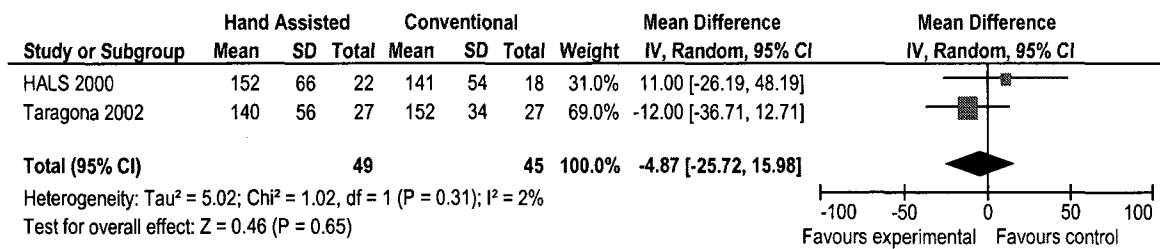
Effects of Interventions:

The main findings from each of the included studies are briefly described:

Operative time

There were no statistically significant differences found when comparing hand-assisted surgery to conventional laparoscopic surgery in any of these parameters; point estimates of risk and associated 95% confidence intervals are reported in figure 3.1.

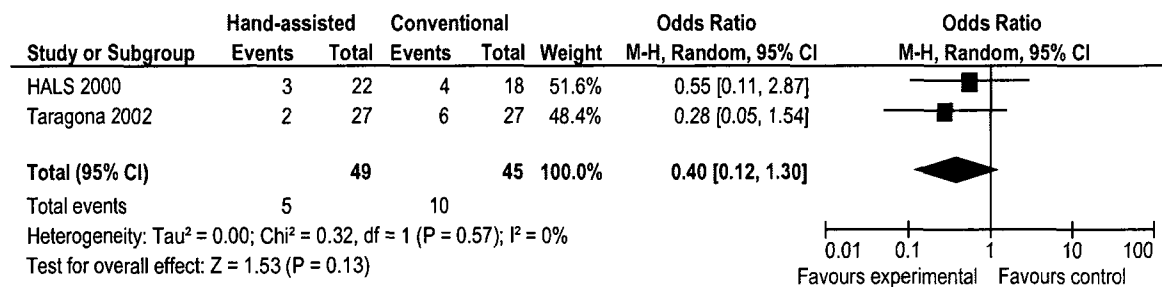
Figure 3.1 Forest Plot – Operative Time



Conversion rate

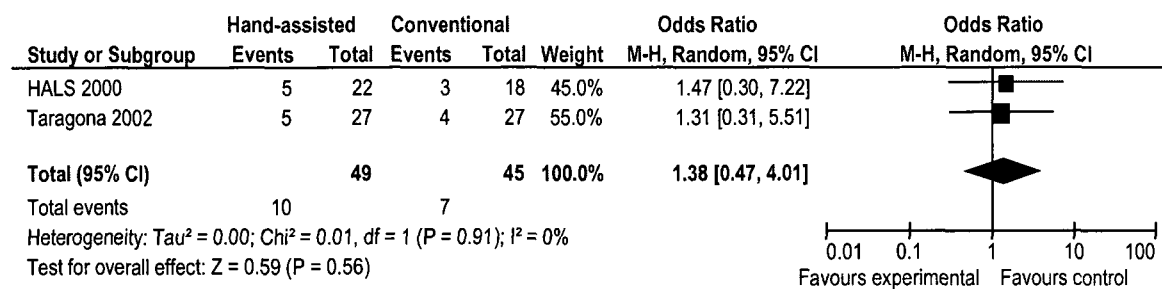
The point estimate for conversion to open surgery was 0.40 [95% CI: 0.12, 1.30]. This is potentially a large effect that would be clinically important. The lack of statistical significance may be due to inadequate power

Figure 3.2 Forest Plot: Conversion Rate



Minor complications (nausea, wound infection/hematoma, ileus) There were no statistically significant differences found. Point estimates of risk and associated 95% confidence intervals are reported in Figure 3.3 below.

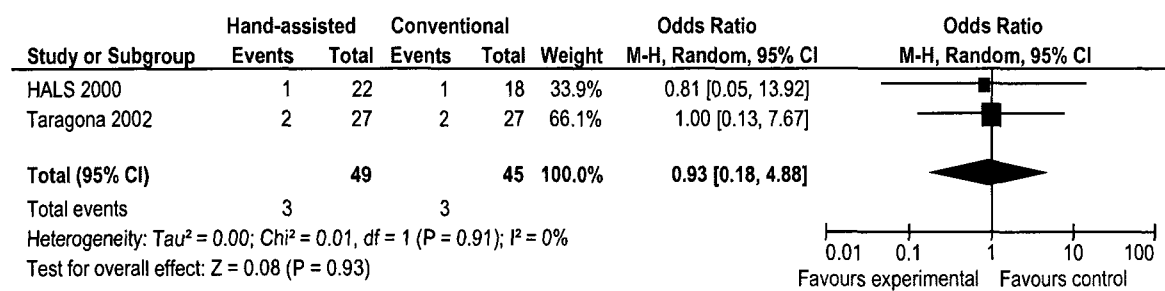
Figure 3.3: Forest Plot – Minor Complications



Major complications (anastomotic leak, GI bleed requiring transfusion, and intraabdominal abscess)

There were no statistically significant differences found. Point estimates of risk and associated 95% confidence intervals are reported in Figure 3.4 below

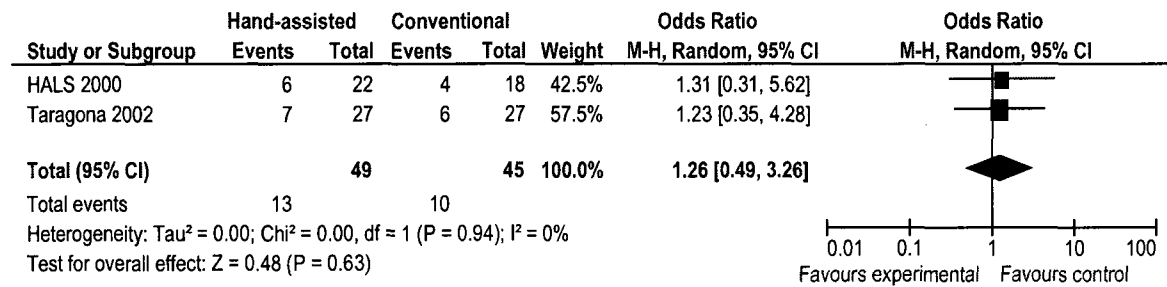
Figure 3.4: Forest Plot: Major Complications



Overall complications

There were no statistically significant differences found. This is not surprising since minor and major complications were similar in the studies. Point estimates of risk and associated 95% confidence intervals are reported in Figure 3.5 below.

Figure 3.5: Forest Plot – Overall complications



Post-operative pain

In the Targarona study¹⁶, no data were provided, but it is indicated that there was no difference in the use of analgesic drugs (whether these were narcotic/anti-inflammatory was not specified) or post-operative pain measures based on use of a visual analogue scale. A description of pain in the post-operative period was used in the HALS group trial¹⁵, which stated that most patients found their pain mild.

Quality of Life

A quality of life measure utilizing the SF-36 was also done by the HALS group demonstrating that physical functioning and general health scores had returned to baseline in both groups.

Bowel function

The HALS group¹⁵ study reported on outcomes on post operative day 1 and 3. They found that a similar percentage of patients in both groups (77% hand-assist and 78% conventional) had return of bowel function by POD 3, with almost all patients (91% Hand-assist and 100% conventional) having a liquid diet on POD 3. The Targarona study¹⁶ found no difference in time to re-feeding (72 hours in the hand-assisted group versus 48 hours in the conventional group).

Length of Stay

There was no difference found in length of stay between the treatment groups in either study – 7.2 days for hand assist vs 6.5 days for conventional in the Targarona paper; 7 days for hand assist vs. 6 days in the conventional group in the HALS group paper.

Mortality

There were no mortalities in either of the studies.

Other outcomes

Lymph node retrieval and cost were examined in the Targarona study¹⁶ and no significant difference was found between the hand assist and conventional laparoscopic approaches.

Discussion

The area of hand-assisted surgery is important. With the return of tactile function it is easier for practicing surgeons to adopt this compared to the conventional laparoscopic approach that is technically difficult¹⁷. In addition, it appears to offer the same advantages of a conventional laparoscopic approach. The conventional approach has been shown to have a significantly longer operative time compared to the open approach¹⁷. It has been suggested that the hand-assisted approach may lead to a similar operative time as the open approach a suggestion that has not been confirmed by this study. This may be due to a lack of power. One potential advantage that is clinically important is decreased conversion rate – although this was not statistically significant it could be a clinically important difference between the two techniques and may not have been apparent secondary to lack of power.

Summary of Main Results:

A total of 2 studies enrolling a total of 94 patients, which assessed HALS versus conventional laparoscopic surgery for colon resection, were identified from our search of the literature. Based on the data available, there does not currently appear to be a

statistically significant difference in perioperative outcomes between hand-assisted surgery and conventional laparoscopy although a potentially important reduction in conversion rate can not be ruled out and would suggest that further trials be done in this area.

Overall completeness and applicability of evidence:

The main limitation of this review is the small number of trials and the small number of patients within these trials; there is a notable lack of power in regard to sufficiently testing for differences in most or all outcomes of primary interest.

Quality of the evidence:

There were some issues with respect to the conduct of the trials, such as calculation of an appropriate sample size and use of adequate allocation concealment. The two studies, as described, do have some clinical heterogeneity as the Targarona study¹⁶ had the vast majority of cases being done for malignant pathology while the HALS study group¹⁵ concentrated on benign pathology and also had some rectal resections included. Patients were also older in the Targarona study¹⁶.

There was no explanation as to how surgeons were chosen to participate in the study i.e. whether a videotape was needed to demonstrate technical expertise. Furthermore, the Targarona paper¹⁶ did not sufficiently describe the standardization of the operative procedure. The postoperative care protocol was not addressed in the HALS group paper¹⁵ and it is possible that there were variations in patient care as eight centers in three different continents were involved (North America, South America, Europe). There was no reporting on whether outcomes were compared between the centers/continents.

The Targarona paper¹⁶ was done at one center and it appears that all patients received similar postoperative care. Despite the limitation and heterogeneity of the identified studies, we thought some relevant clinical information for readers would be obtained by performing a synthesis. The outcomes in both these studies were found to be similar.

Potential biases in the review process:

The aim of having a team involved composed of clinicians and epidemiologists was to minimize bias introduced by the reviewing team. This systematic review was conducted from a protocol which has been published and the hope is that conscious biasing was minimized.

Agreements and Disagreements with other studies or reviews:

There was no other systematic review done regarding this topic when this was written.

Authors' Conclusions:

Implications for practice:

Based on the available data, there is no strong evidence to suggest hand-assisted surgery result in better or worse perioperative outcomes when compared to conventional laparoscopy for colorectal resections.

Implications for Research:

There are few trials examining hand-assisted surgery compared to conventional laparoscopy. Based on existing data, it is difficult to draw definitive conclusions due to the quality of the included studies and the fact that they may be underpowered.

Further studies are needed that have greater power to examine whether there is a difference in operating time, conversion rate and other perioperative outcomes.

Examining conversion rate is especially interesting as it is an outcome that determines whether a patient can potentially benefit from the minimally invasive approach. The point estimate was 0.4 favouring decreased conversion in Hand assist patients but was not statistically significant. This lack of statistical significance may be due to the lack of power.

Another area that future studies should address is the economic viability of HALS, important information for institutions that wish to adopt this technology. The Targarona study included cost during the operation demonstrating no difference but a more detailed and inclusive economic analysis incorporating quality of life measurement in order to report cost effectiveness in the form of an incremental cost-effectiveness ratio would be useful. In addition, there are no studies examining long term outcomes in these patients.

Acknowledgements:

The authors would like to thank the CCCG for their support especially Dr. Henning Andersen for his feedback, suggestions and support

Contributions of Authors:

H Moloo (HM) and R Boushey (RB) conceived the topic for the review. HM drafted the protocol and review and revised it in response to the referees' comments. HM and Fatima Hagggar (FH) screened search results, appraised quality and extracted data from papers. HM, FH, RB, Jeremy Grimshaw, Doug Coyle and Brian Hutton contributed substantially to the intellectual content of the protocol and review, both in terms of the original design and for the revisions.

Declarations of Interest:

None known

Differences between protocol and review:

There were no known deviations from the protocol.

Published Notes:

The protocol has been published by The Cochrane Collaboration. (The Cochrane Review - Issue 4, 2008.)

Table 3.3 Characteristics of studies

	Method/Intervention	Patients	Outcomes
HALS	RCT compare Hand-Assist to Conventional Laparoscopy	Adult, mainly benign, Multicenter (Europe, USA, Brazil)	operating time, incision length, conversion rate, return of bowel function, length of stay, postoperative pain, postoperative complications, quality of life
Targarona	RCT compare Hand-Assist to Conventional Laparoscopy	Adult, mainly malignant, single center (Spain)	operative time, conversion rate, recovery of bowel sounds, re-feeding time, postoperative pain, postoperative complication rates, inflammatory response, lymph node retrieval, relative costs of the procedure

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3.3 Conclusions

From the MISTICC survey it was found that the barriers to a laparoscopic approach were lack of operative time and formal MIS training. Interestingly, while Hand Assist surgery courses and adoption have dramatically increased over the last five years, there is low adoption and interest in this technique in Canada. Proponents of Hand assisted surgery cite decreased operating time, conversion rates, and ease of use and adoption with the return of tactile sensation.

The systematic review did not find significant differences in operating time or other perioperative outcomes although a difference in conversion rate could not be ruled out due to lack of power. In the two randomized control trials there were a total of 94 patients involved and there were some issues with the methodology of the studies. A well designed randomized control trial appears to be needed in this area.

Chapter 4: RCT Protocol for Hand-assisted Laparoscopic Colorectal resections compared to Conventional laparoscopy (with Methodological Discussions)

4.1 Introduction

The systematic review demonstrates that there is a need for more evidence to determine how hand assisted surgery compares to conventional laparoscopy. A well designed randomized controlled trial can provide high quality evidence. To further examine the efficacy of hand assisted laparoscopic surgery, a randomized controlled trial has been designed.

There are methodological issues that are specific to the design of a surgical randomized controlled trial. For example, allocation concealment and blinding in surgical trials pose different challenges as compared to medical trials. Prior to writing the protocol, a review of these issues and possible solutions to them were reviewed.

The following section (4.2) consists of an extended layout of a CIHR proposal with discussion of methodological issues specific to surgical trials interspersed in the protocol. I was the primary author of the protocol with input from multiple individuals including Fatima Hagggar, Brian Hutton and my thesis supervisors. In addition I was primary author for the discussion sections and this was done with input from my thesis supervisors.

4.2 RCT Protocol

1. THE NEED FOR A TRIAL

1.1 What is the problem to be addressed?

Benign and malignant colorectal issues are important and common. Colorectal cancer ranks as the third most common cancer for both men and women in Canada. In 2007, an estimated 20,800 Canadians will be diagnosed with colorectal cancer, and 8,700 individuals will die¹. Complete surgical excision of the tumor provides the only hope for cure and is technically possible in approximately 70–80% of individuals².

There are also many common benign problems of the colon and rectum that require resection – these include diverticular disease, Crohns disease, and ulcerative colitis. Diverticulosis occurs in approximately one third of individuals by age 45 and up to 80% of the population by age 85. A complication (diverticulitis, bleeding, fistula formation) is seen in 10-20% of these individuals².

Two different surgical techniques are available for resection: conventional open colectomy and laparoscopic colectomy. Open colectomy which involves the removal of the pathology via a large abdominal incision, is associated with significant postoperative pain and usually involves a longer hospital stay and prolonged recovery³. The introduction of laparoscopic techniques has revolutionized the field of surgery as a result of the improved perioperative outcomes when compared to conventional open surgical techniques.

Short and intermediate term benefits of laparoscopic colon resection include less post-operative pain, earlier restoration of bowel function, and earlier mobilization of patients³⁻⁵, shorter hospital stay and reduced direct costs⁶. In addition, there is less morbidity from blood transfusion reactions (due to reduced blood loss)⁷, respiratory complications⁸, wound infections⁹, adhesions and incisional hernias¹⁰. A significant improvement in recovery, as assessed by quality of life analyses, was reported two months following laparoscopic colorectal resection in a non-randomized study¹¹ and at two weeks following laparoscopic surgery in a larger multi-institutional randomized controlled trial¹². While some studies have suggested that the laparoscopic approach requires longer operative times, intraoperative complication rates are comparable, and in some studies lower compared to the open technique when performed by experienced surgeons^{3,5,8,9,13}.

One of the obstacles to widespread acceptance was the lack of high quality evidence examining long term survival in cancer patients. Several randomized clinical trials have been conducted to compare long term oncologic outcomes of laparoscopic surgery to open surgery for colon cancer^{3,5,13-15}. These clinical trials demonstrated oncologic equivalence, and in one study significantly better results were observed in the laparoscopic group of patients with stage III disease with respect to overall survival, recurrence and adverse events³.

Despite the numerous benefits of laparoscopy, we have recently completed a recent national survey of practicing Canadian General Surgeons that clearly showed that adoption of these techniques into surgical practice remains low (see Chapter 2). This may

in part be due to the technical difficulty of laparoscopic colon surgery. The procedure requires the surgeon to operate via a camera lens and to move and perform surgery in various technically challenging places without tactile sensation¹⁶. An initial training period is usually required for the majority of surgeons to become proficient in these complex procedures by continuous repetition of these tasks. Thus far, the number of procedures required to reach proficiency in laparoscopic surgery has not been clearly defined¹⁷. However, as many as 62 cases have been suggested for establishing competency¹⁸, which is not feasible to achieve for the majority of surgeons currently in practice. Consequently, surgeons inexperienced in laparoscopy do not routinely offer these techniques to patients and are more likely to convert to an open approach (Chapter 2). Due to the under utilization of laparoscopic surgery for difficult surgeries such as colorectal surgery, some authors have suggested the use of a hybrid technology, hand assisted laparoscopic surgery (HALS), as an alternative¹⁹⁻²⁴.

HALS has been successfully applied to several surgical procedures, including nephrectomy, splenectomy, and hepatectomy²⁵. In HALS, the surgeon can insert a hand into the abdominal cavity through a 7-8.5 cm incision via a specialized hand-assist device while preserving pneumoperitoneum. The hand-assist device is used for sensory perception and to guide the laparoscopic surgical instruments being manipulated with the other hand. With both a hand and laparoscopic instruments, the hand-assist device offers a restored sense of control over the operation. Benefits offered by HALS include the restoration of tactile sensation, the ability to retract surrounding structures, blunt dissection, improved hand-eye coordination, multiple hand exchanges without losing

pneumoperitoneum, and immediate homeostasis if major bleeding occurs. With the exception of the extraction incision being made at the beginning of the surgical procedure and where the hand assist device is inserted, the technique of colonic mobilization and resection are identical for both the straight laparoscopic and hand-assist technique.

To date, only two small randomized controlled trials have compared straight laparoscopic and HALS colectomy^{26,27}. These trials have not demonstrated a difference in operative time. However, the short and intermediate term benefits that have been demonstrated in the conventional approach appear to be conserved when utilizing the hand-assist device. When synthesizing the data from these trials, one difference that possibly exists is a lower conversion rate in patients who are approached with the Hand Assisted method compared to the conventional technique (Chapter 3).

A conversion results when a minimally invasive approach is switched to an open approach (i.e. laparotomy). Conversion rate is an important parameter for surgeons and patients. For the surgeon it usually translates into increased operative time. For the patient, if they are converted to an open procedure then the benefits of a laparoscopic approach are lost. When a surgeon speaks to a patient about the conversion rate when obtaining consent, it gives the patient an indication about the probability of receiving a minimally invasive approach. If this is found to be lower with hand assisted surgery then this potentially has broad implications for what is presently offered to patients.

1.2 What is the principal research question to be addressed?

The primary goal of this study is to examine if there is a difference in operative conversion rates when comparing hand-assisted laparoscopic surgery and conventional laparoscopy in patients undergoing colonic surgery. More specifically, we hypothesize that hand-assisted laparoscopic surgery will decrease the incidence of conversion to an open procedure as compared to that observed using conventional laparoscopy.

Secondary objectives for the study include comparison of quality of life measures in patients undergoing hand-assisted versus conventional laparoscopy and other clinical outcomes during the intra-operative, immediate post-operative and late post-operative periods. Cost-effectiveness of hand-assisted laparoscopic surgery compared to conventional laparoscopy, will also be assessed.

1.3 Why is a trial needed now?

Four conditions justify the proposed large randomized trial: (1) Laparoscopic resections offer patients less peri-operative complications, a shorter length of stay, reduced pain and a more rapid return to normal baseline function as compared to the open technique. However, laparoscopic resections require a significantly longer operating time and are associated with a steep learning curve. These two obstacles were cited in the MISTICC survey (Chapter 2). HALS may overcome these issues, however high quality evidence from randomized trials will be needed for its widespread adoption. (2) There is a paucity of randomized trials for this new technology which may account for the slow adoption

among Canadian surgeons. (3) There has yet to be a high quality economic analysis done evaluating HALS, which is an important piece of evidence for decision makers with regard to the support of this new and costly approach (\$750 per hand port -which are not reusable); high quality evidence gathered in the proposed randomized trial will enable such an analysis to be performed. (4) The impact of this procedure on the quality of life of patients after surgery is a clinically important outcome and will be measured in this RCT; patient-oriented outcomes are not always evaluated in medical research, and yet it is clear that such measures are of great value in regard to determining the value of an intervention.

This trial is designed to be a landmark study in this area and along with the economic analysis that will be undertaken promises to provide surgeons and decision makers in the health care system high quality evidence upon which to base their decisions when contemplating the best technique for colon surgery.

1.4 Give references to any relevant systematic reviews

A systematic review has been performed by the investigators. Two randomized controlled studies^{26,27} enrolling a total of 94 patients (44 undergoing hand-assisted laparoscopic surgery, 50 undergoing conventional laparoscopic surgery) met our inclusion criteria. Clinical heterogeneity existed between the studies with regard to both indication and primary reason for surgery, with one study²⁷ concentrating on malignant pathology and the other consisting of almost exclusively benign pathology²⁶. There were

methodologic flaws in both studies with respect to trial design, specifically regarding sample size calculation and allocation concealment.

Additionally, patients were younger in the study examining benign disease²⁶. Synthesis of the data revealed no statistically significant difference in operative time (WMD: -4.87 minutes, 95% CI: -25.72, 15.98), complication rates (OR: 1.26, 95% CI 0.49, 3.26), or conversion rates to open surgery (OR: 0.40, 95% CI: 0.12, 1.30) when comparing hand assisted surgery to conventional laparoscopy. However the observed potential reduction in conversion rate would be clinically important if born out in larger trials. Since conversion decides whether a patient benefits from a laparoscopic approach, it is an important parameter and determining whether hand assisted surgery can offer a minimally invasive approach to more patients is an important research question. It appears that there is a trend towards decreased conversion rate based on the systematic review (Chapter 3).

Findings from our systematic review demonstrated that the small number of identified trials and their associated methodological shortcomings do not provide a reliable assessment of the role of hand-assisted and conventional laparoscopic resections for colorectal disease. There is a need for additional adequately powered trials to determine whether there is a difference in peri-operative outcomes. The methodology regarding sample size calculation, allocation concealment and post-operative care must be more clearly considered and reported in future trials. Due to significant costs associated with

the use of hand-assist devices, economic analyses are also needed. This trial protocol has been designed to address these issues.

Methodological note: importance of systematic reviews in planning RCTS

To ethically justify a trial, clinical equipoise should exist. There are multiple factors that may contribute to this decision and surgeons' beliefs play a major role in equipoise. It has been suggested that if greater than 70% of practitioners favor one treatment then there is no equipoise²⁸. However, familiarity with existing evidence must also be a step in arriving at this point. Therefore, an investigator should examine the existing body of evidence regarding the question of interest. A systematic review is used to ensure that ample good evidence does not already exist and therefore render the proposed trial redundant.

Fergusson et al did a systematic review on aprotinin and its effect on post operative blood transfusion²⁹. There were 64 trials identified. Unfortunately, after the twelfth trial there was substantial evidence demonstrating decreased transfusion rate with the use of aprotinin compared to placebo with an odds ratio of 0.25 ($p = 0.000001$). It is also important to note that in the remaining trials only 7 cited the results of the largest trial that had been done. To overlook a trial with 1800 patients (28 times the size of the median sized study) seems difficult to justify²⁹.

The best way of examining the evidence that exists regarding a specific question is by doing a systematic review. A systematic review helps an investigator summarize the finding of all the evidence that is available regarding a particular question. Depending on the data available it may also be possible to perform a meta-analysis as part of the review to statistically combine the findings in all the relevant studies and determine if there has been a difference demonstrated between different therapies.

A systematic review has its own nuances and the protocol followed must be designed a priori with rigorous methodology. The methodology is not discussed here but anyone wishing to undertake this should be familiar with the principles involved in doing this type of study and the help of a good biostatistician/epidemiologist can not be overstated.

In an environment where a randomized controlled trial is being done to add unbiased information to the current body of evidence, it would seem entirely contradictory to undertake this without a systematic review. A systematic review should be a mandatory part of an RCT protocol and Research Ethics Boards should ensure that a review has been done prior to approving a protocol and potentially subjecting individuals to a proven inferior treatment (as was clearly done in 52 additional trials examining aprotinin). In a grant proposal when the question of whether a trial is needed 'now' is raised, a systematic review can facilitate the appropriate response (see chapter 2).

1.5 How will the results of the trial be used?

If there is a clinically important decrease in the rate of conversion to open surgery demonstrated with HALS and the known peri-operative benefits of conventional laparoscopy remain including reduced length of hospital stay, complications from surgery and other important outcomes, then there may be an increased interest in the HALS procedure. Surgeons may be able to more easily adopt the HALS technique compared to conventional laparoscopy³⁰, and if these two methods are observed to have similar peri-operative outcomes, it could re-define the way in which colon surgery is performed, as more patients will be able to benefit from a minimally invasive approach.

Economic analysis findings will also be important, particularly in Canada where budgetary constraints are a primary consideration in the adoption of new technologies; if HALS is found to be of a similar cost to conventional laparoscopy, this will also provide an impetus for more centers to utilize this technique. Even if HALS is determined to be a marginally more costly technique, hospital administrations may still support the technology given the emphasis being placed on minimally invasive surgery by both patients and hospital administrations. It could also aid with provincial or national recommendations regarding hand-assisted surgery. Presumably, the technique that can offer the least invasive approach the greatest percentage of the time will be preferred by surgeons, hospitals and patients.

2. THE PROPOSED TRIAL

2.1 What is the proposed trial design?

The proposed study has been designed as a multi-center, double-blind, parallel group randomized controlled trial. This clinical trial will evaluate hand-assisted laparoscopic surgery versus conventional laparoscopic surgery in adult patients requiring left hemicolectomy, sigmoid colectomy, subtotal colectomy or total colectomy for benign or malignant colonic diagnoses in the perioperative and early postoperative period.

Methodological note – Randomized trial as gold standard for evaluating interventions

Randomized controlled trials are the gold standard for evaluating healthcare interventions as they provide an unbiased comparison because randomization is the best method for optimizing the chance that known and unknown confounders are equally distributed across control and experimental groups. Trials of surgical interventions are less common than trials of medical interventions - while the methods of randomized controlled trials are well established for evaluating medical (especially drug) interventions, there remain specific methodological challenges that need to be addressed when planning surgical RCTs.

Methodological note – Trials in surgery

Are trials in surgery addressing the methodological challenges and providing high quality evidence? A study from 2006 identified general surgery RCTs published in six general surgical and four general medical journals in 2003³¹. Of the 69 RCTs analyzed only a third were thought to have done an adequate job: the method by which patients were assigned to different treatments and the way in which blinding was performed was explained in 13%³¹; sample size calculations were performed in less than half of the trials and only a quarter described the parameters involved in the calculation. Failure to conceal allocation can lead to exaggerated effects³²⁻³⁴; sample size calculations are imperative for scientific rigor and to enroll patients into ethically sound trials.

A recent systematic review by Jacquier et al³⁵ was designed to examine if bias is introduced into surgical RCTs and to evaluate the quality of reporting when these trials are published (using a checklist - CLEAR NPT). This review concluded that “inadequate reporting on the management of the surgical procedure, care providers, and surgery center may introduce bias in RCTs of surgical interventions, making their results questionable”³⁵. Another study by Hall et al³⁶ concluded that readers should be cautious when interpreting the results of surgical trials as less than half of the trials made a comment about an unbiased assessment of outcome, gave a description of the randomization technique or provided an estimate of sample size³⁶. The cost effectiveness of treatments under consideration in trials is important to determine the feasibility

of actually being able to offer them as a viable option. Economic issues were addressed in only 6.5% of trials with quality of life examined in 2%³⁶.

Surgical trials have influenced practice and policy³⁷ and cover a diversity of areas. Treatment changes have occurred in:

- breast cancer with less radical surgery³⁸
- melanoma with less radical lymphadenectomy and improved medical management^{39,40}
- esophageal cancer with improved resectability^{41,42}
- carotid endarterectomy by defining its role⁴³⁻⁴⁶,
- hepatobiliary surgery with less invasive management of cancers⁴⁷
- colorectal cancer by defining the role of radiation therapy and minimally invasive approaches^{13,48}

Not all procedures are amenable to a randomized trial. In an interesting study by Solomon and Mcleod, only 40% of treatment questions involving surgical procedures were considered amenable to a RCT approach⁴⁹ and there is a discussion regarding the types of problems that would preclude the initiation of a surgical trial. The main limiting factor identified was: 'most often these would be situations where alternative therapies are unequal in magnitude and at least one therapy is permanent and irreversible'⁴⁹. Although this may be seen as a potential limiting factor for surgical trials, there are trials being conducted that

meet this criterion. For example in the United Kingdom the REFLUX trial is underway comparing a surgical technique to medical therapy in the treatment of gastroesophageal reflux disease⁵⁰.

Another potential barrier in the Solomon paper was that ‘Questions evaluating therapy for malignant disease, comparing surgical with nonsurgical therapies, and where survival was the primary outcome were more likely to have problems precluding RCT’⁴⁹. With regards to these issues, a surgeon may prefer a traditional method of treatment to performing a new one – an old adage in surgery is ‘never be the first or last person to try a new procedure’. Until ample evidence exists, it is difficult to convince surgeons to try a new technique. A good example of this was laparoscopic colon resection for cancer compared to open surgery. This began to be accepted after randomized trials were published demonstrating oncologic equivalency. Speaking to senior surgical staff, convincing surgeons 10 years ago to be part of a trial examining long term survival with laparoscopic colon surgery was unsuccessful and there were no randomized trials in Canada to examine this issue as a result.

Similar to medical trials, when considering the surgical question for a trial it is important to consider whether it is realistic in terms of the frequency of the problem - i.e. if it is a rare problem it may not be practical to pursue a trial due to difficulty obtaining the required sample size. Multicenter trials can offer a way around some sample size issues but there may be trials where the duration

of a trial may be elongated beyond what is practical. For example, to randomize the treatment of pancreatic glucagonomas would be impractical (even with a multicenter trial) where fewer than 250 cases have been described in the literature.

Methodological note – Explanatory vs pragmatic trials

Randomized trials can be categorized by whether they are determining the efficacy of an intervention or its effectiveness. Of course, in many trials, there are elements of both that exist. In an efficacy trial, internal validity (the reliability of the results found within the trial with respect to specific therapies) is given more weight compared to external validity (the applicability of the trial to the real world). The aim of the trial is to determine the change in outcomes with a given intervention under ideal conditions. In a pragmatic (or effectiveness) trial, more of an emphasis is placed on external validity. A pragmatic trial may take into account some of the ‘real world’ problems that may occur. The following table is taken from a paper by Alford ⁵¹.

Table 4.1 Explanatory vs. Pragmatic Trials⁵¹

Explanatory	Pragmatic
Often experimental Setting	Routine clinical environment
Evaluation of efficacy	Comparison of effectiveness
Placebo control	Non placebo control
Control of non specific treatment effects	Non specific effects accepted as part of normal clinical practice
May be better suited to acute conditions	May be better suited to chronic conditions
Patients and practitioners usually blinded	Patients and practitioners not blinded, however allocation to groups should be concealed
May manage with smaller sample sizes	Often larger sample sizes required
Homogeneous group of patients	Heterogeneous group of patients
High internal validity but usually at expense of external validity	High external validity but often lower internal validity
Usually shorter follow up	Frequently longer term follow up
Practitioner skilled in the delivery of the specific treatment intervention	Practitioner skilled in routine clinical practice
Standardized treatment to be issued following rigid protocol	Routine treatment approach incorporating some flexibility to adapt treatment to individual needs
Often one specific laboratory based outcome measure	Usually multiple outcomes reflecting 'real-life' concerns of patient

This trial protocol incorporates elements of both efficacy and effectiveness.

Where possible, a design to demonstrate efficacy has been pursued - especially in the attempts made to blind patients and outcome assessors in the pre and post operative period. The rationale for pursuing efficacy is to minimize bias that could be introduced and affect important secondary outcomes such as length of stay. For example, there may be a bias to keep patients who have had a longer

incision in hospital longer and potentially lead to a longer length of stay for the hand-assist group. Blinding of the outcome assessor, although making the practical running of the trial more complex, will hopefully lead to a less biased comparison of the two techniques. Also, by incorporating measures such as keeping the surgeon blinded for as long as possible and keeping the patient blinded through the perioperative period the objective is to maximize internal validity.

2.2 What are the planned trial interventions?

The surgical procedures being compared in this trial will be standardized in an effort to minimize the potential for the surgical technique to be a biasing factor in the evaluation of patient outcomes. Patients will be randomized into two groups: Group I will include those patients who will undergo a hand-assisted laparoscopic resection, and Group II will include those patients receiving a conventional laparoscopic resection. Details regarding the standardized performance of these procedures are described below in sections 2.2.1 and 2.2.2.

2.2.1 Control procedure – conventional laparoscopy:

Patients randomized to undergo conventional laparoscopic resection will receive treatment from participating study surgeons according to the following surgery guidelines:

- Initial access port utilizing ‘open’ technique;

- Remaining trocars placed under direct vision (the total number of trocars will usually be 4 or 5 but will be left up to the discretion of the surgeon);
- Mobilization of the colon laparoscopically;
- Ligation of vessels may be done utilizing clips, stapling devices, or bipolar vessel sealant devices;
- Division of the distal segment of colon to be done intra- or extra-corporeally;
- Extraction incision will be performed for removal of specimen with wound protector in place;
- Anastomosis may be done intra- or extra-corporeally depending on the site of resection;
- Anastomosis will be done with a stapler (i.e. there will be no hand sewn anastomoses in this study);
- Fascial Defects >10mm in size will be closed.

2.2.2 Intervention procedure – hand-assisted resection:

Patients randomized to undergo hand-assisted laparoscopic resection will receive treatment from participating study surgeons according to the steps outlined for the conventional laparoscopic surgery in section 2.2.1, with the further additions of:

- A hand port will be inserted utilizing a Pfannenstiel incision – the length of the incision is determined by the size of the surgeons hand (usually 7-8.5 cm incision length);
- Mobilization of the colon and other steps outlined in group 1 will be done with the hand-assist device in place.

Methodological note - choice of comparator in surgical trials

The intervention and control procedure and the ethics that surround the selection of the control procedure are important for a surgical investigator to understand.

Placebos have been recognized for a long time. The use of a placebo in a trial enables the investigator to estimate the therapeutic effect of an intervention beyond any nonspecific effect. Use of placebos or active controls has generated a lot of discussion⁵². Emanuel and Miller⁵² described the ‘placebo orthodoxy’ and ‘active control orthodoxy’.

Placebo control advocates point to methodological issues that arise when an active control is used. One issue is that the active control may not be proven to be better than a placebo. As a result, it can be difficult to interpret the findings of a study where no difference is found between the investigational drug and an active control. Sample size is usually higher if an active control is used as the difference between the two treatments is predicted to be less; if the active control is more harmful than a placebo would have been, there is potential for more subjects to be harmed.

The main principal in active control orthodoxy is that whenever an effective intervention exists, it must be used in the control group. The most recent version of the declaration of Helsinki seems to support this: “The benefits, risks,

burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”

It seems that there should be a ‘middle ground’ as Emanuel and Miller have described⁵². The underlying premise of this is that “For clinical research to be ethical, it must fulfill several universal requirements. Among other requirements, it must be scientifically valid and must minimize the risks to which the research participants are exposed.”⁵³. There are situations in which it is unethical to conduct a placebo controlled trial; for example if treatment exists that prolongs life or if subjects assigned to receiving a placebo would more likely suffer serious harm. Alternatively, for ailments that are not serious, if there is only a minimal chance that patients randomly assigned to receive placebo “will suffer harm or even severe discomfort, the use of placebo controls is ethical”⁵⁴.

The footnotes included in the Declaration of Helsinki with respect to placebos support this middle ground as it states that: a placebo controlled trial can be used when an effective treatment exists “Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic,

diagnostic or therapeutic method; Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm” (www.wma.net – accessed Aug 18/08).

Can the ‘middle ground’ exist in a surgical trial? At first glance, it may appear that it is easy for an active control orthodoxy to predominate as patients would require anesthetic (local/general) as well as an incision even if they are given ‘sham’ surgery. One can argue that even with these interventions sham surgery can work within the middle ground ethical framework as outlined above. For example, in a trial examining arthroscopic knee surgery the placebo/sham group had local anesthetic and three 1cm incisions⁵⁵. Furthermore the investigators should be commended for their transparent informed consent where patients were required to write in the chart that: “On entering this study, I realize that I might receive only placebo surgery. I further realize that this means that I will not have surgery on my knee joint. This placebo surgery will not benefit my knee arthritis.”⁵⁵ (although one can debate whether the final sentence is accurate).

Perhaps the most famous studies demonstrating the contribution of utilizing sham surgery were by Cobb et al⁵⁶, and Dimond et al⁵⁷ in the investigation of ligation of the internal

mammary artery in the treatment of angina. These procedures were done under a local anesthetic with patients in the control arm receiving only a skin incision. This study demonstrated no advantage in ligating the internal mammary artery⁵⁷.

There are times where placebo surgery may be questionable as in the trial investigating whether Parkinson's symptoms improved in patients receiving fetal cell implantation⁵⁸. The patients in the control arm of this study had holes drilled in their skulls for the injection but the dura mater was not violated. Although this treatment carries minimal risk, this type of intervention certainly would require a great deal of consideration if trying to work within the Declaration of Helsinki. This study did demonstrate that in five of twenty nine patients in the intervention group, there was worsening of symptoms. The latest data suggest worse outcomes in the intervention group⁵⁹.

As in medical trials, there does appear to be a middle ground in which sham surgery may be able to play a role. The decision to utilize this type of surgery, as with placebos in medical trials, can be guided by the declaration of Helsinki. In this trial protocol, the intervention is compared to an active control.

2.2.3 Consistency in Surgical procedures/Expertise offered

Participating surgeons will be required to have performed a minimum of 20 conventional laparoscopic resections and 20 hand-assisted laparoscopic resections. During the study, a videotape of all procedures performed on study participants will be provided to the study's coordinating center for review by two expert minimally invasive surgeons not otherwise involved in the study to ensure that the procedures being carried out are of an acceptable quality. These measures will be taken in an effort to avoid outcomes being affected by a learning curve phenomenon in these procedures, thereby reducing the possibility of underestimation of the treatment effect.

Prior to study initiation, a meeting will be coordinated with all participating surgeons to discuss both the conventional laparoscopic and hand-assisted approaches to ensure consistency in the type of operation being offered, as outlined in sections 2.2.1 and 2.2.2

Methodological note – expertise/learning curve issues in surgical trials

Learning curves exist with almost all procedures and although Chalmers advocated randomizing the first patient of a new procedure⁶⁰, if early results are examined, there may be a bias against utilizing the new procedure and procedures with great potential may be discarded based on early poor results. One solution to the learning curve is involving surgeons that have already done high volumes of the procedures in question although these surgeons may no

longer have equipoise and may not be willing to randomize patients; a possible solution to this is an expertise based randomized controlled trial.

An 'expertise based' RCT⁶¹ may be applicable when some surgeons have an expertise in one procedure while others have expertise with a different procedure. If laparoscopic versus open surgery were compared in an expertise based trial, surgeons who perform a high volume of laparoscopic surgery would operate on all the patients randomized to the laparoscopic group. Similarly, patients randomized to the 'open' group would be operated on by surgeons who perform this type of surgery the majority of the time. In this type of trial, issues that arise with a learning curve are potentially minimized.

If there are two procedures of which surgeons perform one 90% of the time, there is a great chance that there will be bias against the procedure which is only performed 10% of the time if they are performing both types of surgery in a trial. If the example of laparoscopy compared to open procedures is taken again, the randomized trials on this subject have shown that laparoscopic resections have a longer operating time compared to open surgery. If surgeons who perform open surgery 90% for colon resections are included, this may show an even greater disparity in operating time. A high conversion rate to open surgery may occur as this is what the surgeon is comfortable with and if analysis is done on an intention to treat basis then the potential benefits of laparoscopy may be masked. If expertise is lacking, a proper oncologic

procedure may not be done and this could affect analysis of 5 year survival. It is likely that surgeons prefer the procedure they perform for the majority of patients and unconscious biasing of the trial may occur⁶¹.

If surgeons involved in an RCT are performing both procedures, the surgeons involved should have done high volumes of both in order to minimize the learning curve as a source of bias.

Methodological note - Standardizing procedures in surgical trials:

Two surgeons may perform the 'same' operation but there will be differences in technique. This technique will also vary depending on the number of procedures this surgeon has done. The problem that arises in a trial is which surgeons will participate - surgeons performing a high volume of the procedure under study or those performing an average volume. Including a few surgeons doing a high volume can improve the internal validity however this is likely to be at the expense of external validity.

There are strategies proposed for ensuring a 'minimum standard'^{62, 63}. This includes 'all surgeons involved agree on the performance of critical aspects of the surgery, providing teaching sessions and obtaining documentation that the procedure is performed in a satisfactory manner'⁶². Common sense likely aids in deciding how many surgeons or the type of centers to include: if a procedure

is only being performed in tertiary care centers by few surgeons then it is likely that a trial be conducted in a similar manner.

2.4 What are the proposed methods for protecting against other sources of bias?

Methodological note – allocation concealment

The CONSORT statement⁶⁴ describes allocation concealment as the ‘method used to implement the random allocation sequence (eg numbered containers or central telephone)’. This process should help minimize selection bias; if an investigator is able to determine the process and therefore know which therapy a potential patient could be assigned then he/she can bias this process and one can potentially end up with a nonrandomized trial.

Schulz reports that trials with inadequate allocation concealment have larger treatment effects compared to trials in which the authors described adequate allocation concealment⁶⁵. It is important to note that allocation concealment can and should be done in any trial and is separate from the issue of blinding. It may be impossible to blind a surgeon from the procedure but the method chosen which randomizes patients should be made as difficult to subvert as possible.

The process of randomization is important and the methodology employed does not differ between a surgical and medical trial. Description of various methods

is beyond the scope of this discussion; however there are a variety of methods better than opaque envelopes, alternating patients, chart numbers, etc. Curiosity is natural and patterns may be noticed or incompletely opaque envelopes held up to the light – and once the allocation scheme is revealed bias can be introduced. Poor allocation concealment can ‘defeat’ an RCT and turn it into a nonrandomized trial. Centralized randomization procedures with a computer used for sequence generation make it difficult for an investigator to uncover the process of allocation.

Methodological note: blinding

Once the patient is randomized, an important issue is when the surgeon finds out about what procedure will be performed. Ideally, this should be on the day of surgery to avoid biasing the results. For example, if a surgeon finds out two weeks before a procedure that a patient has been randomized to the choice he/she supports but the patient has multiple comorbidities, there is the possibility of finding a reason for changing the procedure or influencing the patient to withdraw from the study or possibly finding a reason to exclude the patient. This approach appears to be practical and was done successfully in trial comparing laparoscopic and open colorectal surgery with a nurse revealing the intended procedure to the surgeon just prior to induction of anaesthesia⁶⁶. In another trial comparing a laparoscopic and open approach to cholecystectomy, patients were randomized in the operating room to ‘eliminate bias caused by preoperative expectations’⁶⁷.

All efforts should be taken regarding blinding of the patient in a trial designed to examine efficacy. For example if a patient is having a laparoscopic vs. open procedure for a colon cancer resection, a patient may be tempted to push on their abdomen to discern which procedure they have been given. Educating the patient may help ameliorate this issue by explaining during the preoperative period what the study entails and the importance of blinding and why it is done. Further, it could be explained that there is still pain that results from the port sites and the 'extraction' site and that there could be pain in variety of areas and that pushing on one's abdomen is not a reliable method of discovering which approach was used.

In a recent trial ⁶⁷ where a laparoscopic and open technique were compared, the same identical opaque dressings were applied post operatively regardless of the technique used. In the post operative period, a bulky dressing could be applied to the entire abdomen which would not allow the patient to look at the incision and also blunt any pain that is felt when pushing on the dressing.

Efforts should be made to blind the team looking after the patient postoperatively. Incorporating a research nurse as part of the trial team is important – the research nurse need not be blinded to allocation as the team making decisions regarding treatment and discharge would be blinded. This

nurse could examine the wounds to ensure there are no worrisome signs that may require unblinding of the team. Blinding of the team can be difficult – a possible solution is to have a different surgeon or surgical team to care for the patient postoperatively. Most randomized trials are conducted within a tertiary care center with multiple surgeons/multiple surgical teams which makes this possible.

It may seem to be a difficult proposition, however this mechanism already exists at The Ottawa Hospital on the acute care surgery service in which a surgeon operates on a patient but that patient is taken care of by a different team. This same service could be used for the purposes of this trial. To further the objectivity of care and minimize biased outcomes in the postoperative period a clinical pathway should be developed for patients and health care providers to follow – there is a bowel resection pathway already in place at The Ottawa Hospital. Consequently, issues such as criteria for discharge are clearly established or when to advance a patient's diet – this can help protect against bias introduced by health care workers.

After discharge, the length of time for blinding largely depends on practical considerations. In a trial comparing laparoscopy to open surgery it will be evident to that patient what type of procedure has taken place. In a trial where two laparoscopic techniques are compared – for example doing a laparoscopic

repair of a hernia with or without mesh – it is much easier to keep the patient blinded for a longer period of time as the incisions are similar.

2.4.1 Blinding of surgeon prior to and immediately following surgery:

Surgeons will be blinded with regard to the patient's assigned operative procedure until the time of surgery. This will serve to minimize selection bias, as there is a possibility of the assigned type of procedure being changed if the surgeon has earlier notification.

In the immediate post-operative period, an opaque dressing consisting of gauze, abdominal pads and hypofix tape will be applied across the patient's abdomen. Though the incision for the hand port is in the suprapubic area, it is important to consider that extraction incisions associated with the conventional laparoscopic approach will vary from the mid-line, left lower quadrant, or suprapubic areas, and thus there is a need for a dressing encompassing the entire abdominal field. All patients will be placed on a post-operative standardized clinical pathway to eliminate decision making regarding advancement of diet and other post-operative routine care. A research nurse will be used to assess the wounds, and if there are any issues, then he or she will ask a resident from a surgical team not involved with the operation to assess the wound in regard to the need for antibiotics or opening of the wound.

Surgical residents often provide the day-to-day care in the post-operative period in this and other patient populations. These residents are usually assigned to a surgical service

comprised of at least two (and sometimes more) surgeons. The residents assigned to the surgeons on service assist with the procedures these surgeons are involved with, and also take care of these patients post-operatively. This form of arrangement represents an issue in regard to the blinding of physicians during the post-operative period. Consequentially, these patients will be placed under the care of a different general surgery team in the same hospital after their operations. Patient care will not be compromised, as these residents will still be on a general surgery service as opposed to a different subspecialty where they may not be accustomed to taking care of post-colectomy patients.

2.4.2 Blinding of patients prior to and immediately following surgery:

Immediately prior to the time consent is obtained from a patient following explanation of the study's purpose and relevant details regarding treatment and follow-up, it will be reiterated to the patient that he or she will not know what operative intervention they will receive prior to the operation. The consent form for the trial will also clearly state that the patient will be assigned to be treated with, via a randomized assignment process, either a conventional laparoscopic approach or a hand-assisted laparoscopic approach.

Immediately following surgery, an opaque dressing comprising of gauze, abdominal pads and hypofix tape will be used to cover the patient's abdomen. This arrangement will serve to blind the patient at that time as to which sort of procedure he or she received. Blinding will not preclude the provision of essential information given to patients post-operatively with regard to their well-being (e.g. information regarding successful removal

of tumors, if there was any sign of cancer spread, etc). This type of information will be provided to all patients, as it would be unethical to withhold this form of information, which additionally does not affect the blinding process.

There remains the potential for patients to lift their dressing up if they are sufficiently motivated to discover their intervention. However, the importance of blinding will be conveyed to them prior to the operation when meeting with the research nurse. If the patient is experiencing complications that require removal of the dressing, such as required assessment of a wound infection or possible peritonitis, then unblinding will occur.

2.4.3 Blinding of Surgeon and Patient in late Post-operative period

Blinding of the surgeons and patients will not be possible in the later stage of the post-operative period, as the incisions from surgery will be in plain sight, and it will be evident what type of procedure was performed. However, the post-operative care follow-up regimen has been defined, and will not differ between the two groups. Furthermore, unblinding at this time should not have an impact on the assessment of objectively defined late post-operative outcomes such as incisional hernias and small bowel obstructions.

2.4.4 Blinding of Statisticians

The individuals involved with analysis of the study data will be blinded to the identity of the two intervention groups. Unblinding will not occur until after final data analysis has been agreed upon by primary investigators and the steering committee.

2.5 What are the planned exclusion/inclusion criteria?

Inclusion criteria chosen for this study will define eligible patients as those who:

- Require a left hemicolectomy, sigmoid colectomy, subtotal colectomy or total colectomy;
- Are able to tolerate general anesthetic and pneumoperitoneum;
- Are able to provide informed consent for the surgery;
- Are over the age of 18.

Exclusion criteria for the study will deem ineligible patients who:

- Have a history of a past colon or rectal resection; these patients would require a more extensive dissection secondary to adhesions. Additionally, if these patients have a history of colon cancer, then their respective survival curves may be affected.
- Require procedures other than left hemicolectomy/sigmoid resection/subtotal or total colectomy; these patients would be more amenable to a conventional laparoscopic approach, and thus their inclusion in this proposed trial and the associated possibility of randomization to a knowingly inferior therapy would be ethically unjustifiable.

2.6 What is the proposed duration of treatment period?

The treatment in this study is a surgical procedure, thereby making the duration of treatment the time taken to complete the procedure and subsequent follow up.

2.7 What is the proposed frequency and duration of follow-up?

The main objective of this study is to examine a difference in conversion rate and determine if there are any major differences in the perioperative time period. To ensure that early complications are not missed a follow up period of 3 months has been selected. There are no standard follow up protocols for patients with benign/malignant colorectal pathology in the first three months. Patients that have a malignant process will be referred to an oncologist if warranted (i.e. in patients with lymph node positive cancers.

Patient follow-up by the surgeon will be carried out at 2 weeks, and 3 months post discharge. Additional follow up visits will be scheduled if there are complications or other issues that arise that require more frequent visits. Follow-up will also be arranged with the medical oncologist if surgically indicated and with the family physician. Data collection forms will be required to be completed within one week of each follow-up visit. Random checks by the Research Nurse Coordinator will be done to ensure all data forms are being submitted in a timely and accurate manner.

Methodological note: length of follow up

The length of follow up depends on the question being asked in the trial. This trial illustrates some of the issues with determining follow up length. The primary question in this trial is conversion. This is an event that occurs at the time of operation and should not affect outcomes beyond the perioperative period. Discontinuing follow up after 3 months would be reasonable for most of the outcomes that are being investigated.

There are cancer patients in this study and one of the potential secondary outcomes of interest could have been five year survival. To collect meaningful survival data on these individuals would require a longer follow up period. For the practical purposes of using the scarce resources available to fund trials and with respect to the primary objective of the trial 5 year survival was not included as an outcome and this dramatically decreased the need for follow up.

2.8 What are the proposed primary and secondary outcome measures?

The primary outcome of interest, conversion to an open procedure, will be measured at the time the randomized surgical procedure is performed. This measurement is clinically important to both surgeons and patients alike, and is objectively measured. Surgeons wish to offer their patients the most minimally invasive approach possible to ease the burden of recovery. Therefore, if perioperative outcomes such as return of normal bowel

function, days to diet as tolerated, post operative pain and length of hospital stay are similar, the most important issue for surgeons and patients alike would be the probability of receiving a minimally invasive approach. This probability is what is encompassed in the rate of conversion – the rate at which a minimally invasive procedure is changed to an open procedure.

Common reasons for conversion include the presence of bulky tumors and adhesions, or presentation of a case of excessive technical surgical difficulty ⁶⁸; reasons for all conversions to an open procedure in the trial will be captured by case report forms and compared between intervention groups. Some of these issues may possibly be ameliorated through the use of the hand-assist device – the systematic review suggests decreased conversions with hand-assist although it was not statistically significant (OR: 0.40 [95% CI: 0.12, 1.30]).

Secondary outcomes of interest in this randomized trial will include total operative time, quality of life (see section 2.8.1 below), rates of clinically important intra-operative (blood loss, inability to tolerate a pneumoperitoneum or steep positioning, injury to surrounding structures such as bowel, blood vessels, ureter and bladder) and post-operative complications (both surgery related such as anastomotic leak, wound infection, intra-abdominal infection; and, general health related such as thromboembolic event, pneumonia, heart attack, heart failure, stroke), and length of stay in hospital.

Methodological note: importance of defining primary outcome, avoidance of outcome selection bias

A trial must have a primary question. The subsequent trial design centers on this question; without a clear primary question there can be no minimal important difference or any process used to arrive at this difference. Subsequent power and sample size calculations depend on determining this. As stated by Friedman et al⁶⁹, in trials ‘the general objective is usually obvious, but the specific question to be answered by a trial is often not stated well. Stating the question clearly and in advance encourages proper design’. There is a difference in design if the question is “Laparoscopic resection for colon cancer has better five year survival than an open approach’ versus “Laparoscopic resection for colon cancer has the same survival as an open approach’. This former would require the design of a ‘superiority’ trial while the latter would require a ‘non-inferiority’ study – the power calculations and sample size determination are different depending on the underlying design which is dependent on the study question.

The other advantage of having a specific question is to avoid the situation where multiple outcomes are measured and then the outcome(s) that have significant findings or a strong direction in their findings are used as the main outcomes when the study is reported. Having a clearly defined primary outcome a priori maintains scientific rigor and transparency when conducting a trial

An interesting article by Chan et al⁷⁰ examined the completeness of reporting outcomes and consistency between primary outcomes as defined in study protocols and what is published in articles. These authors found that reporting of trials was frequently incomplete⁷⁰. Further, there were issues with biased reporting of outcomes and inconsistency with protocols. They also suggested that trial registration be done to promote transparency in trials and that protocols should be available publicly prior to trial completion⁷⁰.

2.8.1 Determination of quality of life

Two quality of life indices will be administered to patients: a disease-specific, Gastrointestinal Quality of Life Index (GIQLI)⁷¹ and the generic, SF36⁷². Both the SF-36 and GIQLI are widely used and validated. The SF-6D is the version that is used to calculate utilities and is a six dimensional classification that is based on the SF-36⁷³. The SF-6D was valued by members of the general public from the United Kingdom utilizing the standard gamble method⁷³. The SF-6D has utility values associated with its scoring and therefore will be used in calculating the QALYs in this study. The questionnaires will be administered pre-operatively and 2 weeks, 1, 2 and 3 months after surgical resection. This should encompass the time period where one would expect the biggest difference in quality of life to exist. These questionnaires will be mailed out to patients prior to appointments to (1) minimize any changes in feeling that may occur after having a consultation with their physician, and (2) allow it to be completed in the patient's home setting, since responses given in a hospital setting may vary systematically from what the patient would respond in a setting they are accustomed to. Also they may likely to be

more intimidated and less likely to refuse it if required to fill out within the hospital setting.

Methodological note: importance of measuring quality of life and health service utilization measures in comprehensive evaluations

A trial in surgery, the majority of the time, will evaluate how one treatment compares to another. This evaluation usually involves issues such as length of stay in hospital, complications, adequacy of the operation in dealing with the specific problem and survival. One area that has become evident while doing a comprehensive evaluation is the quality of life before and after an intervention.

Wenger and Furberg ⁷⁴ define health related quality of life as ‘those attributes valued by patients, including their resultant comfort or sense of well-being; the extent to which they were able to maintain reasonable physical, emotional, and intellectual function; and the degree to which they retain their ability to participate in valued activities within the family, in the workplace and in the community.’ The different dimensions include physical/psychological/social functioning, overall life satisfaction, perceptions of health status, neuropsychological functioning, personal productivity, intimacy/sexual functioning, sleep disturbance, and pain⁷⁴.

Multiple instruments have been created to measure quality of life – many of these were developed using psychometric methods⁷³ and involve multi dimensional scales. A method distinct from this is one in which preferences and utility measures are used⁷³. The utility measures have been developed through the use of economic theory and incorporate preferences for specific health states and morbidity/mortality improvements to be combined into a single measurement – the quality adjusted life year⁷⁵. The utility measures do not indicate which specific dimension of health related quality of life has been affected but can indicate if there is a positive or negative change.

Incorporating quality of life and economic analysis have become important to understand the overall impact of a new treatment especially in an environment where resources are scarce.

2.9 How will the outcome measures be measured at follow-up?

2.9.1 Baseline Assessment

Performance of baseline data capture will be completed in the clinic at the time of enrollment into the trial. Much of the required information will have been elicited as part of standard data collection prior to provision of informed consent. Once consent has been obtained from the patient, it will be the surgeon and/or research nurse's responsibility to ensure that the form has been filled out completely and correctly in a timely fashion. The baseline case report form will encompass the patient's medical

history including history of present and past illnesses, past surgical history, medications administered, known allergies, and history of social habits (including smoking, alcohol and drug use). Height and weight will also be obtained in order to calculate Body Mass Index (BMI).

All forms will be monitored to ensure they are being accurately and completely filled out. If there are issues that arise at particular centers with regard to accuracy and/or completeness of the forms, these issues will be addressed by the steering committee. As part of the baseline assessment, the patient will also be required to fill out SF-36 and GIQLI questionnaires pertaining to quality of life.

Methodological note: obtaining consent

A physician-patient relationship is one in which the patient may not wish to displease the physician – this is perhaps more pronounced when the patient is going to undergo surgery by the physician (as opposed to prescribing a medication). Therefore, at the time of consent it is imperative that an environment of coercion does not exist. If a trial is being undertaken, the trial should be described to the potential candidate by a research nurse and consent obtained by the nurse as well. In answering questions regarding the study the nurse or research assistant should be trained to give unbiased answers to avoid biasing the patient.

2.9.2 Intraoperative Period

The primary outcome of this study is conversion rate, and this is part of the intra-operative data collection phase. The intra-operative parameters are objective and will be recorded by the healthcare team in the operating room. Two aspects of conversion will be considered for the conventional laparoscopic group: conversion to hand-assisted approach and conversion to open procedure. In the hand-assisted group, conversion to open procedure will be considered using a predefined checklist regarding the reason for conversion. A section within the checklist will also deal specifically with the hand-assist device, as there is literature alluding to issues such as ‘hand fatigue’ and numbness. Although this trial will not determine the ergonomics of hand-assist devices, the information collected will be useful for surgeons and possibly for further improvement of the hand-assist device.

2.9.3 Immediate Post-operative Period

In addition to standard information such as time to discharge, a pre-defined checklist will guide the team in charge of the patient’s care with respect to collection of other complications that may occur post-operatively. A standardized post-operative protocol will be used in the peri-operative period, minimizing the potential for bias when outcome data is collected. The pathway will be important, as there is much variability that can occur during the post-operative care of these patients (e.g. the rate that a patient’s diet is increased, the amount of mobilization of the patient, etc). Length of stay is the most

important immediate post-operative outcome, and with the pathway in place, this should aid in minimizing the amount of bias that the team can introduce.

2.9.4 Late Post-operative Period

As described in section 2.7, the primary purpose of the post-operative follow-up visit is to monitor patients in terms of their progress and to ensure that there are no major issues or complications that need to be addressed

.

For patients with malignant pathology, coordination of post operative care such as referral to a medical or radiation oncologist can be done as well as review of the pathology with the patient. Mortality will also be followed carefully for both groups of patients.

Every patient in the study will receive a call at 2 weeks, 1 month, 2 months and 3 months post operatively (as the phone call will also be necessary to obtain data for the economic analysis). This phone call can also identify if a patient has passed away or if there have been any complications and, as far as possible, an accurate date for these events will be ascertained.

2.9.5 Adverse Events

Anticipated serious adverse events include the risks of an anesthetic, bleeding, infection, anastomotic leak, and general complications such as a thromboembolic event, pneumonia, cardiac event and stroke. To screen for other possible additional complications, at each follow-up appointment, patients will be asked questions regarding any symptoms which they believe could be related to their resection. Since all of these events (e.g. rashes, etc.) may not be anticipated, the feedback from the patient at the follow-up visit will be important. Each occurrence will be reported and its relationship to the procedure will be considered. Time to resolution will also be recorded (or whether there was failure to resolve). A data safety monitoring board would be part of the trial and would help in tracking adverse events.

Methodological note: measuring adverse events in clinical trials

When treatments are being compared (and especially if it is a new treatment) adverse events should be reported. There are general ways in which adverse effects are reported. These can be measured by investigators by 1) reporting whether or not a prespecified adverse event occurred; 2) The severity of an adverse event can be included; 3) the number of times an adverse event occurred in the same patient and 4) the timing of the adverse event in relation to the treatment.

There are also measures of adverse events that are typically used. These have been outlined by Friedman et al as well. These authors describe: 1) the reasons patients are taken off a study medication or have a device removed; 2) the reasons why patients are being given a lower dose of a medication or lower intensity of intervention; 3) type and frequency of patient complaints; 4) lab measurements including radiologic studies; 4) reasons for hospitalizations of subjects; 6) combinations/variations of the previous measures.

2.10 What is the proposed sample size?

The sample size calculation for this clinical trial was estimated based on the formula for comparison of two independent proportions using a chi-square test with a two-tailed α of 0.05 and a power of $(1-\beta)=0.80$. Follow-up in both intervention groups is expected to be close to 100% since the primary outcome, conversion, is one that will be measured during the assigned surgical procedure. There is a small possibility that a patient may be randomized and then for whatever reason not receive any surgical intervention. These patients and the reason for cancellation will be noted; additional patients will then be randomized to ensure that the proposed sample size is met. This should be a rare event and may not occur.

This is a superiority study with the null hypothesis being that there is no difference in conversion rate between hand-assisted surgery compared to conventional laparoscopy for colon resections. A number of the proposed collaborators for this study recently

completed a small randomized controlled trial involving conventional laparoscopic surgery and hand-assisted colectomy, and were able to provide an estimate of their rate of conversion with this technique (hand assisted surgery), which was 2% compared to a 12.5% conversion rate in the conventional laparoscopy group⁷⁶. Surgeons that participated in that study were required to have met the same expertise/training criteria outlined for participation in this study (i.e. performed 20 or more hand-assisted and conventional laparoscopic surgeries), justifying an assumption of a similar rate of conversion in the control group for this trial. The minimal important difference chosen in consultation with a panel of experts for this trial was a decrease in conversion rate of 10%, requiring a conversion rate of 2.5% in the hand-assisted laparoscopic surgery group in this trial to achieve a statistically significant treatment effect. Based on these assumptions, a total of 108 patients per arm or 216 patients in total are required. A recruitment of 10 patients per month, it should take approximately 22 months for recruitment to be complete.

Methodological note: calculating: Sample Size

The ‘power’ of a trial refers to the probability that a trial will actually find a statistical difference in treatments if a difference exists. Power depends on the number of subjects that are included in a study. A sample size calculation is important for determining how many patients are needed to show the difference that has been calculated a priori based on existing evidence – only 11% of surgical randomized trials in a study of trials done were found to give an explanation of this crucial piece of information^{77,78}. With sample sizes not

explained sufficiently it is not surprising that many 'negative' trials in surgery are not adequately powered to find a difference even if it is large since a power calculation may not have been done^{79,80}. The lack of power may also be due to an overly optimistic (or unrealistic) estimate of the difference between treatments. Without proper reporting it is difficult to know where the problem lies. It is important to recognize that the lack of a statistically significant difference in a trial should not be considered evidence of no effect if a trial is underpowered.

It does not appear to be ethical to recruit human subjects into a trial that has not been designed to have enough power to detect a difference (if it exists). There is some debate regarding this as can be seen in an article by Sackett and Cook⁸¹. In this paper there were three main reasons cited as possible uses of small trials. The first is that it can challenge the 'conventional wisdom' that exists. The second is that they can sometimes be 'so definitively positive that they are sufficient to identify the best therapy'. Finally, these trials can be used in a meta analysis⁸¹.

The foundation of the sample size calculation is the minimally important difference (MID) also known as the minimally clinically important difference. For example assume that current ventral hernia recurrence rate in a healthy adult population over a 2 year period is 15%. The minimally important difference would be defined as the minimum decrease in hernia recurrence rates that would

influence a surgeon to switch to a new repair being proposed. There are a variety of methods to arrive at this difference as different surgeons would have different thresholds – different processes to arrive at a consensus of what difference is considered clinically important are well described in an article by Wells et al ⁸².

2.11 What is the planned recruitment rate? How will recruitment be organized?

The study population for this trial will be comprised of patients presenting to general surgeons for elective colon surgery in the tertiary care centers participating in the trial. All centers involved will be tertiary care centers that have been host to a variety of clinical research endeavors in the past. The planned recruitment rate is 10 patients per month based on figures acquired from health record departments at participating centers, and complete accumulation of patients will take place over 2 years. A total of 6 centers will participate in this trial. Therefore this will require approximately 1.5 patients per month for each hospital.

It should be noted that all surgeons participating are members of a division of colon and rectal surgery, and therefore all the cases seen by these surgeons are cases involving either the colon or rectum with a higher number of potential candidates compared to a typical general surgery practice. Clinical rounds will be presented at each of the participating centers prior to initiation of patient enrolment to further promote the trial and increase familiarity with its protocol.

Initial contact with the patients will be made in the general surgery clinic at the time that they are being evaluated. Patients will initially be identified as potential candidates by the surgeon or nurse in the clinic. Then, a research nurse or research associate will go through the study's eligibility criteria with the patient. The individuals selected for this role will be trained sufficiently to give the patient clear and unbiased answers to questions that may be asked. Both study procedures will be described to the patient, as well as the follow-up requirements after the surgery. If the patient decides to enter the study then signed informed consent will be obtained.

2.12 Are there likely to be any problems with compliance? On what evidence are the compliance figures based?

Since the interventions are surgical procedures, compliance issues are not the same as for RCTs involving comparison of medications. Once a subject signs a consent form, the surgery will be done, as these patients require a portion of their colon removed. The surgeons involved utilize both hand-assisted and conventional laparoscopic approaches, and therefore compliance to a minimally invasive approach should not be an issue. To ensure fidelity, all cases will be videotaped.

2.13 What is the likely rate of loss to follow-up?

Since the parameter for the primary outcome occurs in the operating room at the time of surgery, follow-up is not a major concern for the calculation of the sample size. There is likely to be loss of subjects in the follow up period and this will likely lead to a lower number of patients being followed up for the secondary outcomes in the trial. Patients in trials miss clinic appointments at rates that range from 10-84% ⁸³. Prescreening may help decrease the rate of loss to follow up as patient factors such as distance from the treatment center, cultural background, and history of homelessness can affect whether patients return for follow up ⁸⁴, For the purposes of this study, no prescreening will take place as the primary outcome should not be affected and the follow period for some of the secondary outcomes is relatively short.

2.14 Give details of the planned analyses.

2.14.1 Baseline data

Baseline characteristics of patients in the two treatment groups will be analyzed with frequency distributions and descriptive statistics including measures of central tendency and dispersion. All baseline data analyses will be stratified by treatment group.

Methodological results – descriptive analyses vs statistical testing in baseline data

Baseline data is collected on patients to examine whether intervention and control groups in a trial are similar. Randomization should result in similar

groups with respect to measured and unmeasured variables but to examine baseline data still seems prudent. Trials are usually powered to detect differences in the primary outcome and not the baseline data. Descriptive analysis should be sufficient in the majority of trials. If there is concern regarding specific variables between groups that seem unbalanced, statistical testing can be done. It should be recognized that there may not be enough power to detect a statistically significant difference. Similarly, the practice of comparing all baseline data and concluding that the groups are similar because there has been no statistical difference found is a suboptimal approach.

2.14.2 Primary Outcome

Analysis of the primary outcome will be performed on an intention-to-treat basis, thereby making use of the entire cohort of recruited patients. The primary outcome, conversion rate to an open procedure, will first be compared between the two intervention groups using a chi-square test. To complement this approach, and to account for the fact that different surgeons at participating hospitals may be of different skill levels (although all surgeons being recruited are specialized in this area), further analysis will make use of Bayesian, multi-level hierarchical logistic regression modeling. Such an approach allows analysts to account for the hierarchical nature of the data of a multi-center trial, enabling both assessment and inclusion of measures of between-center and between-surgeon

variability, as well as adjustment for clinically relevant covariates that are either imbalanced at baseline or are strong predictors of the outcome. Additional individual variables and interactions will be considered based on clinical importance and empirical data. Per protocol analyses will be performed as secondary analyses to assess the robustness of study findings.

A commonly encountered difficulty in the context of surgical trials is the presence of a *learning curve effect* amongst surgeons over time as the study progresses, and surgeons gain more experience with the procedures being compared. While the impact of a learning curve in this study is expected to be minimal given the decision to restrict participating surgeons only to those that have performed a minimum of 20 of both surgical interventions being compared, the potential presence of a learning curve will be assessed according to the methods outlined by Cook and Ramsey using hierarchical modeling⁸⁵.

Data collection for this study will be designed to include information on a series of commonly used *learning* outcomes of value in surgery trials (including clinical measures such as amount of blood loss and duration of surgery, amongst others) that are considered appropriate measures that enable these analyses to be carried out. If the presence of a clinically important learning curve is detected, statistical analyses will be modified as needed according to recommended methods⁸⁵ to include adjustment for its presence.

2.14.3 Secondary Outcomes

Most of the data from the intra-operative period are continuous measurements, but will also include some measurements based on frequency of occurrence (e.g. number of patients with surgical complications, etc.). A combination of t-tests and chi-square tests will be employed to compare outcomes between groups. A combination of t-tests and chi-square tests will also be utilized for the post-operative data. Quality of life data for both the SF-6D and the GIQLI will be analyzed according to instructions of the scientists responsible for the development of these scales.

2.15 Are there any planned sub-group analyses?

A subgroup analysis will be carried out to compare subjects with a malignant diagnosis and patients with benign disease. Sample size calculations for the study have not been done with this as a goal; however, these groups should be examined to ensure that there does not appear to be a major difference in the primary and secondary objectives, as this would be relevant clinical information for patients, surgeons, and administrators alike.

2.16 What is the proposed frequency of analyses (including interim analyses)?

There is no interim analysis planned as this is not a technology that has been associated with a higher mortality rate or other major adverse events (see chapter 3 - systematic review).

2.17 Will the trial address economic issues?

An economic analysis will be carried out using data collected during the trial. It will be performed from a third party payer perspective, which will serve as a close approximation to the societal perspective. A cost-effectiveness analysis will be done utilizing an incremental cost effectiveness ratio to compare the treatments. (Please see section 4.3 for economic analysis rationale and protocol)

Methodological note: interim analyses

Interim analyses are done to protect subjects that are enrolled. If during a trial one treatment has a dramatically increased benefit or harm it is important to know as randomization would become unethical as the equipoise that existed at the inception of the trial ceases to exist. To maintain objectivity in the process, a data monitoring committee is commonly created with individuals who are independent of the investigators.

An interim analysis may not be needed in trials where an intervention has already been used in the past and has not created any issues that would require an interim analysis. For example, if laparoscopic and open surgery is compared, we know from randomized trials that there are no adverse perioperative outcomes with laparoscopy and that survival is similar. If one were to consider comparing Hand-assisted surgery to either of these (laparoscopy or open

surgery), there is no reason to believe that use of hand-assist would lead to complications necessitating the termination of the trial (and it has already been tested in small randomized trials already).

Certainly, if an intervention is completely novel, then a data monitoring committee with an interim analysis would be necessary.

Methodological note: importance of economic evaluation

Any person involved in health care delivery at any level knows that resources are scarce. This scarcity exists not only in personnel such as physicians, nurses and other allied health care workers but also facilities, operating time, equipment and financial resources. To justify a new treatment within the current environment, there must be an objective approach when deciding on adoption of new technology. Is there an improvement in the quality of life of the patient or improved detection of a health problem? If there is, at what cost does this have associated with it. Therefore, along with testing a hypothesis of whether a new treatment is better with respect to a certain variable, data should also be collected on resource utilization and quality of life.

As mentioned by Drummond et al, the deployment of scarce resources should not be made on 'educated guesses' or 'gut feelings'⁷³. There are three reasons these authors state for the importance of economic analyses: 1) without

systematic analysis, it is difficult to identify clearly the relevant alternatives. 2) The viewpoint assumed in an analysis is important (a program may not look good from one viewpoint but when other viewpoints are considered the program may look much better); 3) Without some attempt at measurement, the uncertainty surrounding orders of magnitude may be critical – an example given by the authors pertains to fecal occult blood testing where six sequential stool tests were recommended by the American Cancer Society. The extra cost per case detected after an analysis was done resulted in an additional 47 million dollars per case detected⁷³.

2.18 What is the estimated cost and duration of the trial?

A three month follow-up is planned. As the recruitment period is estimated to be two years, the plan is to run the trial for 2.5 years. This time period will also ensure that adequate data is collected for the planned economic analysis. The estimated cost for the study is approximately \$327,247 per year.

3. DETAILS OF THE TRIAL TEAM:

3.1 Trial management. Briefly describe the role of each applicant proposed, and indicate if a data safety and monitoring committee will be established and describe its composition.

Day-to-day Management

The Coordinating Centre will be located at the Minimally Invasive Surgery (MIS) Research Group, Division of Surgery department at the University of Ottawa, Ottawa, Canada. Personnel at the MIS Research Group will include the Study Chair, Research Nurse Coordinator, biostatistician, data analysts, and data entry staff. The MIS Research Group will be responsible for the day-to-day management of the trial. Each site will have a Principal Investigator and at least one Research Nurse dedicated to this project. The site Research Nurse will have the responsibility to: 1) screen for eligible patients; 2) seek informed consent from the proxy of the patient; 3) check whether hand-assist devices are available for procedures; 4) accurately fill out all data collection forms.

Role of each applicant

The principal applicants have extensive clinical experience and considerable expertise in the conduct of surgical research and methodology. Members of the research group have internationally recognized expertise in minimally invasive surgery (Drs. Eric Poulin, Joseph Mamazza, Robin Boushey), economic analyses (Dr. Doug Coyle), biostatistics and epidemiology (Dr. Fergusson). Members of the research team have conducted large scale clinical trials sponsored by the Canadian Institutes of Health Research. The Coordinating Centre will manage all data, incorporate rigorous quality assurance strategies, maintain the study database and prepare the final analysis.

The principal applicant will serve as the Study Chair and sit on the Executive Committee of the trial. The Study Chair will have overall responsibility for the project, ensuring the smooth operation of all committees and facilitating communication between member committees. He will have the final approval of all reports and scientific publications emanating from the study and preside over all Executive and Steering Committee meetings. All other co-applicants and the Study Research Coordinator will sit on the Executive Committee (Joseph Mamazza, Eric Poulin, Husein Moloo, Fatima Hagggar, Brian Hutton, Dean Fergusson, Doug Coyle and Jeremy Grimshaw).

All the principal applicants and applicants assume responsibility for the legal and ethical conduct of the research, for the integrity of the research activities and reported data, and for communicating the results of the research recognizing the contributions of the other applicants.

Committees

A Steering Committee and DSMB will be established. The steering committee will be comprised of the Study Chair, site investigators, Study Research Coordinator, and the senior biostatistician. The Steering Committee will have the overall responsibility for the design, execution, and analysis of the trial. The Steering Committee will meet every four months to discuss all pertinent issues. The DSMB will be comprised of a panel of experts

not involved in the trial and will carefully monitor for any major adverse events during the trial.

Methodological note: DSMBs

Data safety monitoring boards are an important component of clinical trials. They ensure that subjects in trials are protected. In addition, clinical trial ‘integrity’ is maintained by examining center data and ensuring that the research protocol is adhered to. All clinical trials require monitoring of some form and a multicenter trial definitely requires a body to oversee the conduct of the trial.

There are guiding principles which have been outlined in the NIH policy guidelines. First ‘the method and degree of monitoring needed is related to the degree of risk involved.’ As much as is practical within the context of a trial, risks to patients should be minimized. The other main principle in the NIH policy is that “monitoring should be commensurate with size and complexity’ of the trial.

Each center involved in a trial is responsible for implementing the requirements outlined in a protocol for data and safety monitoring. The Monitoring board is responsible for ensuring that these centers have done this and continue to do so. The board should be independent of the investigators and sponsors for the trial but should have the appropriate expertise to accomplish the DSMB mandate.

Recommendations for improvement should also be made based on what is being observed.

Based on the fact that the recruitment period is only two years and that both these methods have been safely used, no interim analysis is planned. The DSMB will be ensuring that all adverse events are carefully tracked.

3.2 International collaboration (if applicable). Please discuss the nature of and need for international collaboration.

In Canada, very few surgeons participating in a tertiary institution would meet the minimum inclusion criteria of having 20 cases in both laparoscopic surgery and hand-assisted laparoscopic surgery. Four surgeons from the Ottawa hospital will be participating in this trial and will account for the majority of the cases. However, in order to decrease the amount of time needed to recruit patients and cost for the trial, the study will be done in collaboration with several US institutions where colorectal surgery is offered in both HALS and conventional techniques. Presently, five surgeons from five US tertiary hospitals have agreed to join this trial.

3.3 Please list the proposed participating centers.

The Ottawa Hospital; University of Cincinnati Medical Center, Cincinnati, US; Washington University in St Louis, US; Stony Brook University, New York, US; New York-Presbyterian/Weill Cornell, New York, US; Lahey Clinic, Burlington, US

4. OTHER FUNDING SOURCES

4.1 Provide name(s) and dollar figures for funding being sought from other potential funders, including industry.

Not applicable.

4.3 Economic Analysis

Economic Analysis of Hand Assisted Laparoscopic Surgery vs. Conventional Laparoscopy in Colonic Surgery

Proposal

H. Moloo, J Grimshaw, D Coyle

1.0 Introduction

1.1 Colon Surgery

Before 1991 all colon resections were done via a laparotomy incision. With the development of laparoscopy, surgeons began to perform these surgeries using a minimally invasive approach^{4,5}. With smaller incisions, patients had less pain, shorter stays in hospital, and quicker return of bowel function albeit with a longer operating time^{2,8,13}. Technically, a minimally invasive approach was more difficult and the learning curve long; without tactile sensation to guide the dissection many surgeons were not able to effectively adopt this technique.

A hybrid approach was therefore developed utilizing the hand assist device. This device enabled the surgeon to insert a hand into the patient's abdomen while maintaining the pneumoperitoneum necessary to perform laparoscopic dissection. This approach was found to deliver similar benefits as the conventional laparoscopic method but with decreased operative time and the return of tactile sensation. Many courses have now been developed in the United States to disseminate this technology as it is perceived that surgeons will be able to adopt this technique more easily compared to conventional laparoscopy.

1.2 Current Clinical Practice

After randomized control trials were published demonstrating similar 5 year survival for patients who had laparoscopic colon resections compared to traditional ‘open’ resections many more surgeons have adopted a minimally invasive approach^{2,13,15}. The first study in Canada done reporting on the patterns of practice (chapter 2) has shown that approximately half of Canadian surgeons utilize laparoscopy when performing colon surgery. Six percent of these individuals utilize the hand-assist port. The remaining individuals only perform open surgery.

1.3 Hand Assisted Surgery

Hand Assist ports have been approved for use in Colon and Rectal surgery and has also been approved by The Ottawa Hospital for use (depending on surgeon preference). The incision length associated with the insertion of the hand assist device is 2-4 centimetres longer than the extraction incision utilized in the conventional laparoscopic approach. Studies thus far have shown that the benefits of the minimally invasive approach are maintained (although there is a slightly larger incision).

Currently, the hand assist device has a higher cost associated with it at a cost of \$800.

1.4 Rationale for Study

There have been two randomized trials examining Hand-Assist compared to conventional laparoscopy^{26,27}. Neither has undertaken an economic analysis. Minimally invasive colon surgery is an area that continues to expand as randomized control trials have demonstrated its benefits; additional information regarding this newer hybrid approach is important to surgeons and hospital administrations as it is a method through which practicing surgeons may be able to offer patients the benefits of laparoscopy without the steep learning curve and increased operative time⁷⁶. With scarce resources, waiting lists are becoming a problem across Canada and if the operating time can be decreased then this may play a small part in alleviating this.

Understanding whether the additional cost associated with the device is offset by the benefit of decreased operative time (and possible decreased length of stay) is important. For centers that are planning on initiating a minimally invasive colorectal approach, this information would be essential for administrative purposes and the decision as to whether to fund these devices.

Length of stay has been examined in the setting of randomized control trials and there has been no difference found with regards to this^{26,27}. The median length of stay for patients who have minimally invasive colorectal surgery in our group is 5 days based on a review of our 14 year database. Median operating time varies with procedure but for all colorectal cases is just under 3 hours.

1.5 Objective

To assess if hand assisted colon surgery is cost effective compared to conventional laparoscopy.

2.0 Study Design

2.1 Study Question:

Is HALS cost effective when compared to conventional laparoscopy for colon resections in an adult population?

2.2 Study Population:

Any individual who requires a colon resection of the left, sigmoid colon or subtotal/total colectomy. These locations are where approximately 40% of colonic resections take place and are also suited to the amenability of utilizing the hand assist device. Subjects who have had a previous colon resection will be excluded due to the increased technical difficulty (and increased complication rate) that arises with previous operation.

2.2 Justification for Choice of Treatment Comparators:

Many surgeons at The Ottawa Hospital and across Canada perform minimally invasive colon resections with the advantage of decreased length of stay and lower morbidity rates compared to an 'open' procedure. Any operation performed on a subject in this study would utilize a minimally invasive approach.

The use of a hand-assist device has been shown to confer the benefits associated with a laparoscopic approach. In addition to providing tactile sensation to the surgeon, operative times have been shown to be decreased in some studies. This method is an approach that surgeons may be able to more readily learn as opposed to conventional laparoscopy which is technically more difficult and may allow more patients to benefit from the minimally invasive approach. Although the hand-assist device requires an incision that is 2-3 cm longer than the extraction incision that is required in conventional laparoscopy, the incision with the hand-assist device is usually placed in a less noticeable area (it is in the suprapubic area compared to midline).

2.3 Target Audience

Surgeons performing colorectal surgery

Decision makers in the ministry of health and in hospital administrations

3.0 Perspective of Study

3.1 Choice of Perspective

A Third Party Payer perspective has been chosen as the recovery period is expected to be similar between the Hand-assist and conventional laparoscopy group. Even when comparing conventional laparoscopy to hand-assist there appears to be no major difference after six weeks postoperatively. A Third Party Payer should be a close proxy for the Societal perspective. As a result, there will be no measurement of time spent by family members helping post operatively and no measurement of time lost to patients as a result of hospital appointment. Outcomes such as these are expected to be similar and it is felt that this would make the logistics of the study much more complex and expensive with minimal return in terms of additional valuable information.

3.2 Justification for Choice of Perspective:

The cost to the health care system appears to be the most important perspective since it encompasses the majority of costs that are associated with this surgery. Increased length of stay, operative costs, the cost of the hand assist device and additional clinic visits, all are paid for by the government.

Both operative techniques employ a laparoscopic approach and based on the experience we have from our institution and available data, there should not be any significant difference in return to function and patient and caregiver times.

As a result, the perspective will be that of a Third Party Payer as the analysis considers the cost to the health care system.

4.0 Analysis

4.1 Form of Analysis

A Cost Utility Analysis will be used and the two groups will be compared utilizing the Incremental Cost Effectiveness Ratio (ICER). This type of analysis seems to be ideally suited for this trial since there is no information on the overall costs of the hand assist approach compared to conventional laparoscopy and quality of life is an important consideration in any patient undergoing surgery. In this study, it would be interesting to determine if the slightly longer incision in the Hand-Assist option affects quality of life.

4.2 Analytic Horizon

It is expected that most perioperative complications would occur in the first three months after surgery and this will be the chosen analytic horizon.

5.0 Outcome Measures

5.1 Reporting

Costs will be reported in Canadian dollars.

Effectiveness will be reported in Quality Adjusted Life Years ⁷⁵

5.2 Costs

The costs for surgery have been divided into four different time periods: 1) preoperative, 2) operative, 3) immediate postoperative and 4) late postoperative.

Data for costing will be obtained through a variety of methods. For the operative and immediate postoperative periods, it will rely on accurate information obtained from the surgeon, O.R. records, and patient records. For the late postoperative period, costing will rely on data gathered at clinic visits and phone calls to the patient every 1 month along with any records for the patient existing within The Ottawa Hospital (from the vOACIS system).

Costs will be calculated based on market prices in year of completion of study and as per initial therapy assignment. Discounting will be done at a rate of 5% as recommended by the CADTH⁸⁶

5.21 Preoperative Period Costs

Costs in this period will not be calculated. There are no additional investigations, bloodwork, etc. that are required with either of these methods

5.22 Operative

The operative costs center around the following relevant resources:

Surgeon Fee, Anesthesia fee, Operating room costs, hand assist device cost, disposable instrument costs

Surgeon Fee:

Measurement of Relevant Resource: The procedure performed will be recorded by the surgeon – this will either fall under the category of Subtotal colectomy, Total colectomy, Left Hemicolectomy or Sigmoid Colectomy.

Valuation/Costing of Resource: Obtain from OHIP Schedule of Benefits ⁸⁷ – at present time there is no difference in surgeon fee with regards to whether the hand assisted approach is used compared to the conventional laparoscopic approach. The current fees are the following and 25% is added for any case that is done using a minimally invasive approach:

Total Colectomy with Ileorectal Anastamosis: \$1242.90

Left Hemicolectomy: \$1082.95

Sigmoid Colectomy: \$799.55 (in addition if there is mobilization of the splenic flexure during a sigmoid colectomy an additional \$102.40 is added to the fee.

Subtotal Colectomy and Ileostomy: \$1057.70

Anesthesia Fee:

Measurement of Relevant Resource: Obtain from OHIP Schedule of Benefits ⁸⁷ – the cost for the Anesthetist will depend on the duration of the surgery

Valuation/Costing of Resource: Anesthesia fees are calculated based on units of time – each unit of time representing 15 minutes. There is also a base amount of units given for each case and the number of units increases as the duration of surgery increases: for the first hour of a case for every 15 minutes 1 unit is given. For the second hour it is 2 units for every 15 minutes and for the third hour onwards it is 3 units. The base unit payment for the procedures is the following:

Total Colectomy with Ileorectal Anastomosis: 9 units

Left Hemicolectomy: 8 units

Sigmoid Colectomy: 7 units

Subtotal Colectomy and Ileostomy: 7 units

Therefore the total billing for the Anesthetist will be the Base Units + Units calculated on duration of surgery.

Operating Room Costs:

Measurement of Resource: This will be obtained from the Ontario Case Costing Project⁸⁸ – the longer the time for the case, the higher the fee.

Hand Assist Device Cost:

Measurement of Resource: This will be obtained from the current market price in The Ottawa Hospital from the manufacturer (U.S. Surgical)

Valuation/Costing of Resource: Currently, the device costs \$725.00 per device

Disposable Instrument Use:

There are a variety of disposable instruments that are used during laparoscopic surgery. These include the harmonic scalpel, the Ligasure, endoscopic and regular staplers, and clip appliers. The use of these may vary between the two approaches. For example, with the hand-assisted approach 'regular' staplers (staplers that are used in open surgery) can be used instead of the more expensive endoscopic staplers (designed specifically for laparoscopy). Similarly, with the return of tactile sensation and the ability to control hemorrhage manually the possibility exists that hemostatic devices such as the Ligasure or Harmonic scalpel may be utilized at a higher frequency in the conventional laparoscopic approach.

Measurement of Resource: The number of disposable instruments used including the number of staplers (and number of reloads of staplers used) will be recorded for each case.

Valuation/Costing of Resource: The costs will be obtained at the current market price. These are all recorded in the operating operational budget and are accessible through the operating room charge nurses. For most of the resources that will be used, the costs are the following:

Ligasure: \$750.00

Harmonic Scalpel: \$719.60

Endo Universal 65: \$300.00

Endo Universal 65 Reload: \$50.00

Endo GIA: \$200.00

Endo GIA Reload: \$36.00

TA60: \$100.00

GIA60: \$100.00

GIA80: \$155.00

EEA: \$300.00

Alexis Wound Retractor: \$55.31

5.23 Immediate Postoperative Costs

These costs center on the following:

Length of Stay:

The longer the length of stay, the higher the expense. These patients are usually cared for in a regular ward room on a Surgical Floor. To estimate this cost, the Ontario Case Costing project will be used to obtain estimates for a cost per bed day for a general surgical ward and an ICU stay.

Measurement of Resource: The length of stay for each patient will be recorded including length of stay on the general surgical ward and length of stay in the intensive care unit.

Valuation/Costing of Resource: The Ontario Case Costing project will be utilized to obtain estimates. The latest estimates available are the following:

If patients are readmitted to hospital for a complication secondary to the surgery after being discharged initially then the length of stay for that admission will also be costed in a similar manner.

Need for Reoperation:

Recorded (as per the outline thus far) and the additional operation would be costed.

Complications:

The cost of much of this would be accounted for in the length of stay data. However, complications that require an intervention (i.e. a percutaneous drain for an abscess) would be costed – this type of complication is rare. Consultation fees from other specialists would also be included if assistance is required in the management of complications postoperatively.

Measurement of Resources: Procedures performed in hospital will be recorded. Consultations from different specialties will also be recorded (i.e. Cardiology consult for atrial fibrillation)

Valuation/Costing of Resource: This will be calculated based on the latest version of the Ontario fee schedule.

5.24 Late Postoperative Costs

The late postoperative costs center around the following relevant resources: Additional clinic visits, additional non-surgical interventions, emergency room visits, readmission, Homecare, and re-operation.

During this period, the patients will be seen in the clinic for regular visits as described. In order to capture the data needed for the economic analysis phone calls will be made to each subject at 1 month intervals to gather information regarding the identified relevant resources in this time period.

Information will also be obtained during this time period with regards to the time patients returned to work.

Cost of Additional Clinic Visits:

The RCT design stipulates that the subjects be followed up at 2 weeks and 3 months. There is no standard follow up at the present time for these patients and this regimen may be more or less intensive depending on surgeon preference.

Measurement of Resource: All Clinic visits will be recorded for each subject.

Valuation/Costing of Resource: Clinic visits will be costed based on: 1) surgeon fee from fee schedule depending on what is done in clinic and 2) use of clinic (obtain from Ontario Case Costing project).

Cost of Additional Non-surgical Interventions:

Patients may require a variety of interventions depending on complications post operatively. This could include procedures such as endoscopy and percutaneous drains.

Measurement of Resource: Any non-surgical intervention performed in relation to the colectomy/complication of colectomy will be recorded. Therefore the intervention along with the reason for the intervention will be recorded for each subject.

Valuation/Costing of Resource: These can all be costed based on the OHIP fee schedule.

Cost of Emergency Room Visits:

If complications do arise, it is likely that patients will visit the Emergency department.

Measurement of Resource: All emergency room visits will be recorded along with the reason for emergency room visit. If the patients are seen at The Ottawa Hospital then these will be obtained from the computerized patient record. Any ER visits occurring outside The Ottawa Hospital will be sought from the patient during the phone call or clinic visit. In addition, if patients are seen for a surgery related problem in the ER, a dictation/emergency record from the physician seeing the patient would sometimes be sent to the surgeon.

Valuation/Costing of Resource: These visits will not be microcosted keeping the budget of the trial in mind - the Ontario Case Costing Project will be utilized to estimate the cost/visit to the ER.

Cost of Readmission:

Any surgical complication leading to readmission such as a small bowel obstruction will also be measured and costed as for the initial hospitalization as outlined above.

Cost of Homecare:

If there are complications such as a wound infection or prolonged use of a Foley catheter then Homecare involvement will be necessary. If this occurs, Homecare usually corresponds with the surgeon with regards to the treatment necessary and when treatment is stopped. In addition, this data will be sought with the phone calls and at clinic visits.

Measurement of Resource: Any homecare required for the patient will be recorded along with the duration of homecare.

Valuation/Costing of Resource: Costing for this will be obtained by contacting the Homecare office regarding cost/nurse visit and the number of visits that were required.

Cost of Reoperation:

The main reasons for reoperation in the late post operative period would be secondary to small bowel obstruction, recurrence of cancer/stricture, and hernias. These would be costed with a similar approach as outlined above

5.3 Effectiveness in QALYs

Two questionnaires will be given to patients: one disease specific questionnaire and the other a generic questionnaire which facilitates calculation of utilities. This will be done prior the surgery as well as postoperatively at 2 weeks, 1, 2 and 3 months.,.

The SF-36 is the validated generic questionnaire with utility values that will be used to evaluate quality of life. The SF-6D is the version that is used to calculate utilities and is a

six dimensional classification that is based on the SF-36 (ref Brazier). The SF-6D was valued by members of the general public from the United Kingdom utilizing the standard gamble method. The SF-6D has utility values associated with its scoring and therefore will be used in calculating the QALYs in this study. In order to use the SF-6D the SF 36 must first be filled out (or the SF 12 and three additional questions from the SF 36).^{73,89}.

The Gastrointestinal Quality of Life Index is the disease specific questionnaire that will be used and does not have any utility values associated with it⁷¹. It is validated for gastrointestinal surgical procedures^{71,90,91} and therefore will be used to detect if there are significant differences in patient outcomes based on this instrument. These results will be compared to the results from the SF-36.

5.4 Discounting

QALYs will be discounted at a rate of 5% as is recommended by the CADTH⁸⁶. There are different discount rates used in other countries but as mentioned the CADTH guidelines are being followed. In addition, sensitivity analysis will be done with different discount rates.

6.0 Analysis

6.1 Incremental Cost Effectiveness Ratio

The main form of comparison with regards to hand-assisted surgery versus conventional laparoscopy will be done by determining an incremental cost effectiveness ratio .If one of

these treatments is more effective with lower costs then it will be considered the dominant treatment. These results will be presented to surgeons/policy makers by presenting the costs for each treatment. The quality of life scoring will also be presented for each treatment. Finally the incremental cost per QALY will be presented to the target audience. By presenting the results in this fashion it should be easier to understand how the ratio is being calculated. Sensitivity analysis will be carried out as outlined in section 6.2. .

6.2 Simple Sensitivity Analysis

This will be carried out on the following variables:

1) Cost of Hand Assist Device

This will likely decrease in the future and is important to consider

2) Cost of disposable instruments

These are important during laparoscopic surgery and as technology in the laparoscopic field continues to increase, these prices will likely decrease

3) Cost of surgery

If the cost of hand assist surgery is decreased compared to the conventional laparoscopy fee, this could affect the overall cost-effectiveness. Currently, all minimally invasive approaches cost 25% more compared to the open surgical technique of resection.

4) Discounting

Additional analysis will be done with discount rates of 0% and 3%

5) Length of stay

The length of stay in these patients is already fairly short considering many of these individuals are elderly and have comorbidities. Scenarios in which length of stay is decreased could also be examined.

6) Quality of Life

A sensitivity analysis will be done assuming there is no difference in quality of life

6.3 Stratified Analysis

This would be important for this trial with the two variables to stratify on being age (usually weaker tissues in the elderly) and the diagnosis (benign vs malignant diagnosis as patients with cancers usually have higher conversion rates to open procedure). This may identify a subgroup of patients who should always be offered the hand assisted approach.

6.4 Uncertainty Regarding Parameter Estimates

There will be uncertainty around the various parameter estimates from the trial.

The Bootstrapping method will be used to deal with this issue. Bootstrapping is a method of resampling and will be used to derive standard errors and confidence intervals from the data that has been obtained from the trial. By utilizing the distribution of values that exists in the data collected, the bootstrap method will resample a multitude of times (i.e. ten thousand times) and will provide a more precise estimate of a parameter.

7.0 Interpretation of Results

The results will be reported in terms of ICER. They will be interpreted in order to give an indication of whether the extra costs at the time of operation for the hand assist device are an effective use of scarce health resources for minimally invasive colonic resections

8.0 Study Limitations

This is not a true Societal Perspective as the Third Payer perspective should be a good proxy for the Societal perspective and there will be additional data collected with respect to time to return to work. Productivity losses and costs to caregiver are not calculated but should be similar for both groups.

As stated earlier there is no standard of care for follow up in this group of patients. With the follow up regimen (including phone calls) this is likely more rigorous follow up compared to normal practice and may result in more investigations.

With regards to the quality of life measurement, since a generic instrument is being used it may not be sensitive enough to detect a difference between groups (if a difference exists)

4.4 Conclusion:

In chapter 2, the MISTICC survey demonstrated that surgeons may not be adopting minimally invasive techniques based on technical difficulty and increased operative times. One modality that may provide the benefits of conventional laparoscopy is hand assisted laparoscopic surgery – this may be easier for surgeons to adopt due to the tactile sensation that is returned and proponents of this method state that this may also reduce operative times. To compare conventional laparoscopy and hand assisted surgery, a systematic review was done which concluded that more high quality evidence is required to decide if there is a difference between these methods. This protocol provides the framework for this type of trial and the methodological explanations provide the rationale behind the decisions made regarding the design.

Evidence based surgery is important and randomized controlled trials are an important part of this. When experimenting on human subjects a surgeon can not justify obtaining

consent from a patient for a trial with poor design. The meticulous care that surgeons take in the operating room must be extended to the conduct of clinical trials.

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Epub 2006 Sep 14

Chapter 5: Conclusion

The MISTICC survey demonstrated that laparoscopic colorectal resections are a well accepted alternative to the open approach. There has been good uptake of this method although it appears that there is a low volume being done. The major obstacles to performing laparoscopic resections are lack of training and operating time.

The systematic review which compared hand assist laparoscopic surgery to conventional laparoscopic surgery demonstrated a paucity of high level evidence. There are two randomized controlled trials which have compared the two techniques but they suffer from a lack of power (with a total of 94 patients) and have some methodological issues. One interesting finding from the review was the possibility of a decreased conversion rate with the hand assisted technique. An economic analysis is also needed in this area as the hand assist device is expensive.

The findings of the systematic review served as an impetus to design a protocol for a randomized controlled trial comparing hand assist to conventional laparoscopy; a protocol was also designed for an economic analysis. The design of a surgical trial requires that a number of issues be carefully considered and therefore the protocol was written in an extended CIHR format in order to incorporate discussion sections addressing the challenges of surgical RCTs.

The MISTICC survey gave a good snapshot of what is occurring nationally with regards to laparoscopic colorectal surgery and this had not been done prior to this study.

Potential weaknesses relate to potential response bias with surgeons more interested in laparoscopy responding although this may have been compensated partially by recently qualified surgeons being excluded (surgeons with less experience were more likely to use laparoscopy) due to the method of obtaining the mailing list. Some questions could have been stated more clearly especially the question regarding the number of procedures done per year – it refers to ‘abdominal’ cases and it would have been better to specifically ask about ‘colorectal’ cases.

The robustness of the results from the systematic review is limited by the number of studies available for analysis, the small number of subjects and the heterogeneity of the studies. This will hopefully change and there has been a further study published since this systematic review was written.

The extended CIHR format that was used in the protocol facilitated the examination of the methodological issues in surgical trials. There are a multitude of issues in surgical trials and the discussion undertaken in this thesis does not address every issue. In addition, more detail could be written about every issue that was addressed. The hope is that a surgeon could read the discussion and use it as a good starting point for gaining a better understanding of surgical trials and some of the crucial steps involved.

This thesis has raised a number of questions that could be answered with future research. From MISTICC, more research is needed to find methods to deal with the lack of operating time and formal training that are barriers to adoption of laparoscopy. Hand

assist could potentially help with both these issues and the application of this technology is an interesting area for further study. Other methods to impart MIS to practicing surgeons are also important to examine. There are also regional variations in Canada that require a closer look.

The systematic review has clearly shown that further trials are needed to examine the role of hand assisted surgery. An RCT is challenging to perform and would likely require a multicenter approach to obtain the sample size needed in an adequately powered trial. An interesting question is whether hand assisted surgery should only be offered in the context of a randomized controlled trial – this may encourage more surgeon participation.

While raising questions and creating new challenges for the future is something that this thesis has done, it is also hoped that it has made a contribution to the existing literature and knowledge that exists about this topic and hopefully will present a platform from which to contribute to knowledge in the future.