

**PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY**

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Jon Ivar Einarsson, MD, PhD, MPH

PROTOCOL TITLE

A Partners prospective study assessing the perioperative outcomes of common methods of minimally invasive contained tissue extraction

FUNDING

None

VERSION DATE

1/13/2016

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The goal of this study is to compare common methods of tissue extraction at the time of minimally invasive surgery, including vaginal extraction and mini-laparotomy; both performed within a containment system. The primary aim is to assess return to normal daily activities after each of the surgical techniques. Return to daily activities will be recorded on a post-operative patient activity diary recording the following tasks: a) work (if applicable), b) domestic tasks, c) driving a vehicle (if applicable) and d) physical exercise (if applicable). Additional information regarding post-operative pain (measured on a Likert scale), potential complications of each technique, such as tearing of the bag or leakage, and peri- and post-operative outcomes will be collected.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Laparoscopic approaches to gynecologic surgery are generally accepted as enabling superior visualization of the abdomino-pelvic cavity, smaller incisions, reduced blood loss and decreased recovery time relative to surgeries performed via laparotomy^{1, 2, 3}. A common method of tissue extraction is laparoscopic power morcellation. Power morcellation systems have been

frequently employed in laparoscopic surgery, and effectively core the desired tissue into pieces that are small enough to be removed via the cannula in laparoscopic trocar ports.

On 4/17/14 the FDA issued a statement discouraging the use of power morcellation. The FDA released further guidance on 11/24/14 that encourages alternatives to laparoscopic power morcellation for women with symptomatic uterine fibroids, such as vaginal or abdominal specimen removal and laparotomy using a smaller incision (mini-laparotomy). Given the recent limitations on use of power morcellation, manual morcellation via vagina or minilaparotomy with use of a knife blade are the only options which allow for large specimen removal at the time of minimally invasive surgery. This study will compare two methods of manual morcellation: vaginal extraction and mini-laparotomy incision. Although the techniques for vaginal or minilaparotomy morcellation have not typically involved use of a containment bag as standard of practice, we plan to perform all morcellation procedures within a containment bag system in an attempt to minimize any risks associated with tissue disruption or dissemination.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This study is designed as a prospective cohort study. The primary aim is to assess return to daily activities after the two methods of tissue extraction. Secondary aims include evaluating peri-operative outcomes and incidence of spillage of the morcellated tissue or fluids in the abdomen and pelvis.

We anticipate enrolling a total of 70 adult women scheduled to undergo a laparoscopic Hysterectomy. Power calculation was based on a previous study which assessed recovery time in total laparoscopic hysterectomy and supracervical laparoscopic hysterectomy²⁰. Using a study power of 90% and an alpha level of 0.05, we concluded that we would need 28 patients for each tissue extraction group (vaginal extraction and mini-laparotomy) in order to detect a mean difference of 5 days in return to daily activities, and an additional 14 patients to account for anticipated 25% loss to follow-up. This will be a multi-center trial with surgeons participating at Brigham and Women's Hospital, Faulkner Hospital and Massachusetts General Hospital. Our goal for enrollment is 70 subjects with the first 35 subjects included in a mid-point analysis.

Inclusion criteria include women 18 years of age or greater who are eligible to undergo laparoscopic Hysterectomy, as determined clinically by the operating surgeon. Other concomitant laparoscopic procedures will be

performed as indicated and at the discretion of the primary surgeon (e.g., lysis of adhesions or removal of an ovarian cyst).

In all cases, exclusion criteria will include suspected malignancy, medical illness precluding laparoscopy, inability to give informed consent, or allergy to indigo carmine or methylene blue dye.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Subjects in this research study will undergo laparoscopic hysterectomy. Tissue extraction for hysterectomy patients will be performed via vaginal extraction with knife morcellation or mini-laparotomy incision with knife morcellation. All procedures will be performed within a containment system (bag). The choice of procedure will be determined clinically by the operating surgeon based on patient characteristics and patient preference.

Vaginal extraction with knife morcellation in bag

Vaginal extraction with knife morcellation will be done in the standard fashion with the specimen being placed in a containment bag with the addition of 5cc of either indigo carmine or methylene blue dye.

Vaginal extraction will be limited to total laparoscopic hysterectomy when a colpotomy (vaginal opening) is already made as part of the procedure. After the uterus is completely amputated from the vagina, a gloved sponge will be placed in the vagina to maintain pneumoperitoneum. A specimen retrieval bag of appropriate size will be introduced into the abdominal cavity via one of the abdominal ports or via the vaginal opening. The specimen will be placed in the bag and the opening of the bag brought out through the vaginal introitus, making sure that the whole circumference of the bag opening is exteriorized. With a syringe attached to an elongated aspirator tip, 5cc of either indigo carmine or methylene blue will be injected into the dependent portion of the bag with care to avoid spilling outside the bag. A self retaining Alexis-type retractor may be placed inside the bag to aid with retraction. It is recommended to maintain pneumoperitoneum within the abdomen during the morcellation process to aid with keeping viscera away from area of knife morcellation. Knife morcellation will then proceed in the standard fashion until the specimen is removed.

Mini-laparotomy incision with knife morcellation in bag

Mini-laparotomy incision with knife morcellation will be done in the standard fashion with the specimen being placed in a containment bag with the addition of 5cc of either indigo carmine or methylene blue dye.

A 2-5 cm mini-laparotomy will be made either at suprapubic or umbilical location. Upon abdominal entry, a self-retaining Alexis-type retractor or gel port single-port device is placed. The specimen retrieval bag is then placed intra-abdominally through the mini-laparotomy. A cap is placed over the retractor or port to maintain pneumoperitoneum. Switching back to laparoscopy, the specimen is then placed into the bag and the opening of the bag is brought out through the mini-laparotomy, making sure that the whole circumference of the bag opening is exteriorized. 5cc of either indigo carmine or methylene blue will be injected into the dependent portion of the bag with care to avoid spilling outside the bag. The retractor may be placed inside the bag to aid with self-retraction. It is recommended to maintain pneumoperitoneum within the abdomen during the morcellation process to aid with keeping viscera away from area of knife morcellation. Knife morcellation will then proceed in the standard fashion.

In all cases, following morcellation and removal of the bag, the abdomen and pelvis will be carefully examined for any signs of spillage of fluid, tissue or blue dye as well as the integrity of the containment system by the surgeon. After surgery the bag will be carefully examined for any tears or damage. The used bag will be emptied, washed, dried, and filled with blue dye-tinted fluid (indigo carmine or methylene blue). The bag will be filled to the level where it was inside the patient during morcellation, as noted by marking pen during morcellation process (ie: any portion of bag exterior to patient during morcellation process will not be assessed).

If there is leakage noted prior to morcellation, the specimen will be removed and a new containment system will be replaced. If there is trauma to surrounding structures (bladder, bowel, blood vessels) during morcellation, the procedure will be discontinued. Conversion to laparotomy may be performed to repair these structures.

After Surgery

After surgery, patients will complete a report of their recovery symptoms in a diary including a report of pain, medication use and activities. They will fill out this diary daily until their post-operative visit or the day they return to perform their activities (work, household chores, driving and exercise) without limitations (exactly the same way they used to do before surgery, as determined by a pre-operative baseline diary), an estimated 2-4 week time frame.

Post-operative Visit

As per routine post-operative care, the patients will return for a post-operative office visit between 2 and 6 weeks after surgery. This will include a

discussion of recovery and exam as appropriate. Patients will return their diary at this time if they have returned to normal activities.

Follow-up

Patients who had not yet returned to all of their activities by the post-operative visit will receive a package either in person or in the mail including a pre-paid envelope for them to return when they have resumed all activities. A phone call reminder will be made 2 weeks after sending the package.

All data will be analyzed using SPSS. A member of the team (such as a research assistant who has been trained in HIPPA procedures) will be in charge of abstracting data from the medical records and entering this information into a study database.

The following data points will be collected via the intraoperative data collection sheet: surgeon, patient MRN, date of surgery, hospital (BWH, FH, MGH), procedure (total hysterectomy, supracervical hysterectomy), approach (laparoscopic, robotic), method of tissue extraction (vaginal, mini-laparotomy), size and location of mini-laparotomy if applicable, indication (pain/endometriosis, abdominal bleeding, fibroids, prolapse, other), length of procedure (incision to close), time for morcellation (insertion of bag to removal of bag), type of bag (EcoSac, LapSac, Lahey Bag, EndoCatch, Anchor tissue retrieval, Alexis Contained Extraction System), use of bag protector, use of indigo carmine or methylene blue, bag breaking/tearing/leaking and spillage of dye or tissue fragments.

The following data points will be extracted from the medical record: race, age, gravidity, parity, BMI, prior abdominal surgery (LSC, Laparotomy, None), pathology, weight of specimen, chromopertubation, intraoperative complications and estimated blood loss, concomitant procedures, hand-assisted, cystoscopy (for hysterectomy), and adnexal surgery (for hysterectomy). Post-operative complications will be assessed 8 weeks after surgery and rated using the Clavien-Dindo scale. Outcome information including EBL >1000ml, bowel injury, bladder/ureter injury, transfusion, conversion to open, reoperation, readmission and length of stay will also be collected.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

On 4/17/14 the FDA issued a statement discouraging the use of power morcellation. The FDA document includes language that acknowledges the fact that surgeons have offered morcellation in closed systems (i.e. a bag) and it does not recommend against this technique. The most recent FDA

guidance released on 11/24/14 allows for uncontained power morcellation in women who are not peri- or post-menopausal.

Our study protocol is more conservative than the current FDA recommendations with the addition of a containment bag to minimize spread of tissue when performing manual morcellation with a knife blade.

Women who choose not to participate in this study will receive traditional care as determined appropriate by patient and physician discussion.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The risks to subjects are minimized by use of a tissue containment system during morcellation. There have been no reported risks of dissemination of tissue morcellated in an enclosed containment system.

Risk of trauma to surrounding structures is minimized in a containment system as the specimen and scalpel is away from vital structures.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

We have been performing in bag morcellation since early 2014, and the events of tissue and dye spillage have been minimal. Should an unforeseen adverse event arise that appears likely to be related in any way to the study, the principal investigator will review cases, consider halting study and report the event to the IRB. Potential adverse events include vascular or visceral injury associated with the morcellator device, spread of tissue and leakage of dye or tissue.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The participants are undergoing a surgically indicated procedure and all surgeons are experienced at performing laparoscopic hysterectomies and laparoscopic myomectomies. Subjects will not undergo any additional

treatment as part of this study other than scheduled surgery. The study procedures will not cause any additional discomforts.

There is a theoretical risk for tissue dissemination if the bag tears or breaks. The use of a containment bag does not pose an additional threat to women undergoing vaginal extraction or mini-laparotomy incision, and represents an additional safety step over traditional practice in cases of vaginal or minilaparotomy morcellation.

There have been no studies evaluating risk of indigo carmine dye spillage; however there have been reports of a pressor effect with use of indigo carmine. Diluted indigo carmine dye has been used for chromopertubation (evaluation of the patency of fallopian tubes). There have been no reported reactions during these procedures. There have also been no studies evaluating the risk of methylene blue dye spillage. Diluted methylene blue has also been used routinely for chromopertubation. There have been no reported reactions during these procedures. Thus, if there is spillage of dye into the abdomen or pelvis, risk of a reaction is theoretically low.

There is the possibility that the process of keeping a diary about pain and return to daily activities will cause subjects discomfort.

There are no other foreseeable risks or discomforts to subjects. Should an unforeseen adverse event arise that appears likely to be related in any way to the study, the principal investigator will halt the study and report the event to the IRB.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Patients enrolled that undergo laparoscopic morcellation in a containment system (bag) may experience traditional benefits of minimally invasive surgery. These include, but are not limited to, lower incidence of complications, such as infection, hemorrhage, deep venous thrombosis and pulmonary embolism, incisional hernias, postoperative adhesions. We hypothesize that patients who have vaginal morcellation will experience earlier return to normal activities compared to mini-laparotomy. The effect on operating room times is unknown. Moreover, the results of our study may provide the investigators with valuable information to facilitate the creation of an ideal morcellation containment system to be used in future gynecologic laparoscopies. A greater understanding of alternatives to laparoscopic power

morcellation (vaginal extraction and mini-laparotomy incision) will be gained and may benefit future patients.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The study population of women will be derived from the population that is seeking laparoscopic Hysterectomy at Brigham and Women's Hospital, Faulkner Hospital, and Massachusetts General Hospital. All cases of laparoscopic hysterectomies and myomectomies will be eligible. The first 35 eligible cases will comprise the subset for mid-point analysis. Patients with a known allergy to indigo carmine or methylene blue will be excluded from the recruitment.

This is the same population that stands to potentially benefit from this research.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

There are no plans to exclude non-English speaking subjects from this research project. When potential non-English speaking subjects are encountered, the hospitals' translator services will be asked to assist with explaining the study and obtaining informed consent. The PHRC policy on Obtaining and Documenting Informed Consent of Subjects who do not speak English will be followed.

For guidance, refer to the following Partners policy:

Obtaining and Documenting Informed Consent of Subjects who do not Speak English
<http://healthcare.partners.org/phsirb/nonengco.htm>

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about

participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruitment begins at the initial consult visit. The surgeon will explain the study, and then ask the patient if they would like to hear more about it. Only patients that affirm that they are interested will then be given a description of the study protocol by the surgeon and will be given a copy of the consent form to take home with them. A research assistant will contact the patient approximately one week after their initial appointment to confirm if the patient is interested in enrolling in the study and to answer any outstanding questions about the study. If the patient is interested in participating, informed consent will be obtained by a physician investigator prior to surgery.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

There is no remuneration available for this study. There are no additional hospital-related expenses anticipated as a result of patient participation in this study, as all visits described are within the standard guidelines for routine surgery.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects

<http://healthcare.partners.org/phsirb/recruit.htm>

Guidelines for Advertisements for Recruiting Subjects

<http://healthcare.partners.org/phsirb/advert.htm>

Remuneration for Research Subjects

<http://healthcare.partners.org/phsirb/remun.htm>

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Once a patient agrees to take part in this study, she will be screened, and if she is eligible, and agrees to participate in the study, the informed consent will be obtained by a physician investigator. The patient will keep a copy of the consent form and the signed original copy will be held on file.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:

<http://healthcare.partners.org/phsirb/newapp.htm#Newapp>

For guidance, refer to the following Partners policy:

Informed Consent of Research Subjects

<http://healthcare.partners.org/phsirb/infcons.htm>

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The principal investigator will review and investigate any study-related complications as they occur. An analysis of the data will be performed as necessary pursuant to any complications observed, and at the mid-point of the study. The primary investigator will be in charge of deciding if the study should be stopped based on these analyses. There will be continuous monitoring of events by the principal investigator and prompt reporting of complications to the IRB and all other study physicians, in accordance with the study's Data and Safety Monitoring Plan (DSMP). The principle investigator will also keep track of investigator deviations in terms of informed consent processes and study procedure, and all repeat deviations will be reviewed.

Any unanticipated problems involving risks to subjects or others including adverse events will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC unanticipated problems reporting guidelines. Adverse events will be reported according to pre-established guidelines such that the relationship of the risks and benefits to subjects

participating in research studies remains acceptable throughout the conduct of the study. Reports of unanticipated problems involving risks to subjects or others will be tracked on an adverse event tracking log and submitted through Insight/eIRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem. Adverse events and minor deviations tracking logs will also be maintained in-house.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

There are no foreseeable risks or discomforts to subjects. Should an unforeseen adverse event arise that appears likely to be related in any way to the study, the principal investigator will halt the study and report the event to the IRB.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The principal investigator will perform continuous monitoring of any events and report problems to the IRB and other appropriate bodies as needed.

All surgeons involved in this study will be responsible for completing correct operative data collection at the time of surgery, as well as during the post-operative period. A minimum number of persons will be involved with the data abstraction in an attempt to decrease introduction of bias. The research assistants will also keep a copy of all source documents such as informed

consent on file, and informed consent must be revisited in discussion with the patient on the day of surgery prior to subjecting her to study protocol.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance

<http://healthcare.partners.org/phsirb/datasafe.htm>

Adverse Event Reporting Guidelines

http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

With regard to risk of disclosure of confidential patient information, all possible precautions will be taken to ensure the confidentiality of study data. Specific precautions include keeping all identifying information in password protected computer systems or in locked filing systems accessible only to study staff.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

No specimens or data will be sent outside of Partners.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

No specimens or data will be stored outside of Partners.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

No specimens or data will be received from parties outside of Partners.

Official Title: A Partners prospective study assessing the perioperative outcomes of common methods of minimally invasive contained tissue extraction

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