Protocol Number: FAS-101
Version 1.0 - 25 November, 2020

Evaluation of the impact of fascial closure technique on post-operative pain in patients undergoing Pfannenstiel incision for Caesarean Section: A Randomised Trial

Protocol

Sponsor:

DAN Women and Babies Unit
Sunnybrook Health Sciences Centre
2075 Bayview Avenue, Toronto, ON
M4N 3M5

Conduct: This clinical trial is being conducted in accordance with International Conference of Harmonisation guidelines on Good Clinical Practice and the ethical principles originated from the Declaration of Helsinki. It is confirmed that the Clinical Trial Protocol meets the applicable regulatory requirements.

Contact List

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Principle Investigator's Agreement

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the DAN Women and Babies Unit with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: FAS-101

Protocol Title: **Evaluation of the impact of fascial closure technique on post-operative pain in patients undergoing Pfannenstiel incision for Caesarean Section:**
A Randomised Trial

Protocol Date: 25 November 2020

Principle Investigator:
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_____ Nov. 26, 2020

Signature of Principle Investigator Date

PROTOCOL SYNOPSIS

TITLE	Evaluation of the impact of fascial closure technique on post-operative pain in patients undergoing Pfannenstiel incision for Caesarean Section: A Randomised Trial
SPONSOR	DAN Women and Babies Unit, Sunnybrook Health Sciences Centre
FUNDING ORGANISATION	DAN Women and Babies Unit, Sunnybrook Health Sciences Centre
NUMBER OF SITES	1
RATIONALE	Caesarean sections are the most commonly performed surgical procedure throughout the world. Within the Canadian population, approximately one-third of all deliveries occur via Caesarean section. Chronic pain post-operatively has been identified as an issue that a large proportion of patients suffer with. As a result, a variety of surgical techniques have been undertaken, with some being compared to ascertain the reason for this chronic pain. One method which has been observed is related to the fascial layer and associated pain related to this layer. Whilst the abdominal fascia plays an integral role in ensuring the abdominal contents remain in situ. A variety of methods have been employed and studied to ensure the integrity of the fascial layer to reduce the risk of dehiscence, but no studies undertaken to date have evaluated the method of fascial closure and their effect on post-operative pain.
STUDY DESIGN	Randomised, double-blind, three-arm trial
PRIMARY OBJECTIVES	1. Analgesia use 2. Pain score between three groups
NUMBER OF SUBJECTS	350
SUBJECT SELECTION	Inclusion Criteria: - Women aged 18-60 years - Women with singleton pregnancy - Patient undergoing elective lower segment Caesarean section via a Pfannenstiel Incision - Use of Regional Anaesthesia (epidural or spinal anaesthesia) Exclusion Criteria: - Multiple pregnancy - Patient undergoing non-elective Caesarean section - Caesarean section through midline laparotomy incision - Patients undergoing Caesarean section under General Anaesthesia - History of chronic pain - History of post-operative complications (haematoma, abscess, dehiscence, re-operation)

ARMS AND INTERVENTIONS	Participants will be blinded to which method of fascial closure will be undertaken at the time of their surgery. 1. Single suture, knot above rectus fascia 2. Two sutures, knots above rectus fascia 3. Two sutures, buried knots below rectus fascia
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be enrolled in the study for 10 weeks. Screening: 1 day Treatment: 1-2 days (subjects will be admitted to hospital) Follow-up: 10 weeks The total duration of subject recruitment time is 6 months, with subsequent follow-up over a 10-week period after initial recruitment.
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	1. Analgesia use in first 72-hour period post-operatively. 2. Pain score questionnaire results over 10-week post-operative period.
STATISTICS	
Primary Analysis Plan	Statistical analysis will be undertaken using IMB® SPSS® Statistical Software ver. 26 to undertake a two-sided T-test comparing group 1 vs. 2 and group 1 vs. 3 to assess for statistical significance in analgesia use and pain scores.
Rationale for Number of Subjects	Based on a power of 80% at an alpha of 0.05, we estimate a 15% reduction in pain scores. As a result, we require a total of 255 subjects in this study. Given an estimated drop-out rate of 35%, we aim to recruit a total of 350 participants. In addition, sub-group analysis will be undertaken comparing pain scores between primary and repeat Caesarean sections. Based on the same power of 80% at an alpha of 0.05, with an estimation of a 15% difference in pain scores, we require a total of 140 subjects for this sub-group analysis.

LIST OF ABBREVIATIONS

CS	Caesarean section
CPCSP	Chronic Postsurgical Caesarean Section Pain
CPSP	Chronic Postsurgical Pain
CSEA	Combined Spinal-Epidural Anaesthesia
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EPCS	Elective Primary Caesarean Section
ERCS	Elective Repeat Caesarean Section
GCP	Good Clinical Practice
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LSCS	Lower segment Caesarean section
PI	Principle Investigator
SAP	Statistical Analysis Plan
VAS	Visual Analogue Scale

1 BACKGROUND

Caesarean sections (CS) are the most commonly performed surgical procedure worldwide, with approximately one-third of all births occurring via Caesarean section in developed nations,(1-3) and over of 40% of deliveries in some nation such as Brazil(4). Specifically in the United States of America, this equates to nearly 1.3 million deliveries in 2016(4, 5). Given the difficulties associated with women undergoing a CS, coupled with expectation of recovering from a large surgical procedure whilst caring for a newborn present new challenges to the mother and her family.

Opioid analgesia is a common staple for post-surgical analgesia to aid in recovery.
Unfortunately, due to the increase in Caesarean Section rates(1-3), there is more reliance on opioids to manage pain(6-9). This unfortunately is wrought with difficulties given the side-effect profile of opioid analgesics as well as their addictive potential(7). As a result, the reliance on alternative measures including surgical technique to minimise opioid requirements is an area of clinical research which requires further development(6, 9).

Anaesthetic technique and post-operative pain management play an integral role in post-operative pain. Another avenue which has been explored relates specifically to surgical techniques(2, 3, 5, 10-12). Studies have evaluated the type of incision(2, 3), method of skin closure(5), and closure of the peritoneum and its impact on post-operative pain(1). Specific to closure of the rectus fascia, Kahkhaie et al. evaluated the type of suture material used during Caesarean section and found their impact on post-operative pain(10). Finally, Trimbos et al. evaluated methods of fascial closure following midline laparotomy(12). Whilst these studies outline multiple surgical techniques and have shown impact on the risk of developing CPSP, no studies were found which directly compared the technique by which the fascia is reapproximated at the time of CS via a Pfannenstiel incision.

The purpose of this protocol is to outline our study evaluating three methods of closure of the rectus fascia and their effect on post-operative pain in patients undergoing lower segment Caesarean sections (LSCS) via a Pfannenstiel incision in a Canadian tertiary care obstetrical unit.

2 STUDY RATIONALE

LSCS are the most commonly performed surgical procedures worldwide. Given that much of the development of surgical approaches for trainees is based on the centre at which they are trained, there is no standardised approach which offers superiority as it relates to specific steps in the procedure. Given these issues, the notion of an evidence-based approach to fascial closure which minimises post-operative pain would be superior as it relates to the patient's return to normal activities, duration of analgesia use and overall quality of life. It is for this reason we aim to undertake this study comparing three methods of rectus fascia closure during LSCS at our unit to ascertain if there is an impact on patient's post-operative pain.

2.1 Hypothesis

Our study hypothesises that the presence of a thicker knot in the subcutaneous layer when closing the rectus fascia leads to more irritation of the cutaneous nerves causing more sensitivity and perceived pain by the patient. In addition, we also hypothesise that by burying the knot under the rectus fascia at the angle of the rectus incisions will further diminish the level of nerve irritation in the subcutaneous layer and will allow for a further reduction in perceived pain and analgesia requirements.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective in this study is to evaluate post-operative pain in patients undergoing elective lower segment caesarean sections via a Pfannenstiel incision. The intervention in question relates specifically to the method by which the rectus fascia is closed. Participants will fill in a pain questionnaire over a period of 10 weeks at set intervals to ascertain their level of pain on visual analogue scores and requirements for analgesia.

3.2 Secondary Objectives

Our secondary objective relates specifically to whether there is a difference in pain in patients undergoing primary or repeat caesarean sections. This will also be determined using sub-group analysis of participant pain scores based upon their questionnaire responses.

4 STUDY DESIGN

4.1 Study Overview

The proposed study will be designed as a double-blinded, randomised, single-centre, clinical trial. Participants will be randomised into one of three groups based upon which method of rectus fascial closure will be undertaken. Post-operative questionnaires will be undertaken over a 10-week period at set time points to elucidate post-operative pain.

4.2 Strengths and Limitations

The overall strength of this study lies in its randomisation of participants as a means of minimising bias. In addition, we aim to achieve a statistically significant result which can specifically target the efficacy of these three specific techniques in fascial closure and its impact on post-operative pain. As a result, this study will help to determine if a standardised method of fascial closure is more effective as it relates to post-operative pain when patients undergo a Pfannenstiel incision during their Caesarean section.

With respect to limitations, this study only considers the use of a Polysorb^{TM} absorbable sutures (Covidien^{TM}) as the suture of choice in closure of the rectus fascia given this is the primary suture which is used in our unit. It does not consider the use of other suture materials including delayed absorbable monofilament sutures and their impact on post-operative pain. In addition, given the subjectivity of pain perception, we accept that this may impact our findings given participants

will have varying perceptions of their pain. We hope that by randomising our participants in each group, this will help to standardise our sample across all three groups.

5 SUBJECT SELECTION

5.1 Study Population

Our study population includes all women undergoing elective primary or repeat lower segment Caesarean sections via a Pfannenstiel incision at Sunnybrook Health Sciences Centre in Toronto, Canada. This is a tertiary care centre with approximately 4000 deliveries annually and a Caesarean section rate of 18%. The average rate of Caesarean sections in most developed countries is approximately one-third of all deliveries.

5.2 Sample Size

Our sample size is based upon a power of 80% at an alpha of 0.05 based on a two-sided t-test comparing groups. Based on these findings, our total sample size in each arm is 85 participants. In total, as there are three arms, our total sample size requires 255 participants, whereby randomising 85 participants to each group. In addition, we aim to undertake a sub-group analysis comparing primary to repeat Caesarean section with a power of 80% at an alpha of 0.05. Once again, a two-sided t-test would be used and based on these findings, we would require a total sample size of 140 participants, whereby comparing 70 participants per group. Given these minimum requirements and we estimate a drop-out rate of approximately 35%, we aim to recruit a total of 350 participants to this study.

5.3 Inclusion Criteria

1. Women aged 18-60
2. Singleton pregnancies
3. Patients undergoing elective LSCS via Pfannenstiel incision
4. Use of regional anaesthesia (epidural, spinal anaesthesia, or combined spinal-epidural)

5.4 Exclusion Criteria

1. Multiple pregnancy
2. Patient undergoing non-elective CS
3. Caesarean section through midline laparotomy incision
4. Patients undergoing CS under general anaesthsia
5. History of chronic pain
6. Post-operative complications (haematoma, abscess, dehiscence, re-operation)

6 PROPOSED INTERVENTION

All participants will undergo a lower segment Caesarean section via a Pfannenstiel incision. All participants involved in this study will undergo some form of regional anaesthesia (epidural, spinal, or combined spinal and epidural anaesthesia). Participants requiring general anaesthesia will be excluded from this study. Subsequently, the procedure is carried out and the delivery of

the foetus is undertaken. The hysterotomy is closed and haemostasis is then ensured in the intra-abdominal cavity. At our unit, the peritoneum is not re-approximated.

Our proposed intervention involves three separate methods of closure of the rectus fascia which will be directly compared. Please refer to **Appendix A** to view diagrams outlining each method of fascial closure:

1) The first method of fascial closure involves the use of one #1 Polysorb™ Polyglactin 910 braided absorbable suture (Covidien™). At one angle of the rectus fascia, both the anterior and posterior leafs are grasped using Bonney forceps and the suture is tied behind this angle. This suture is then used to re-approximate the fascia in a continuous fashion across the incision. Prior to completing the suturing of this layer, the contralateral side is grasped with a Kocher clamp to bring the fascia forward so that the suture can be tied to itself behind the contralateral incision.
2) Method two involves two separate #1 Polysorb™ braided absorbable sutures (Covidien™). Both leafs of the rectus fascia are grasped using the Bonney forceps and the suture is placed behind the angle of the incision above the rectus fascia. Subsequent to this, the rectus fascia is reapproximated in a continuous fashion until the suture reaches the contralateral rectus abdominus muscle. Subsequently, a second #1 Polysorb™ suture is tied behind the contralateral angle in the same fashion and the remainder of the rectus fascia is reapproximated in a continuous fashion until both sutures are met, whereupon they are tied together.
3) The final method again involves two separate #1 Polysorb™ absorbable sutures (Covidien™). Both leafs of the rectus fascia are grasped with the Bonney forceps and the suture is placed behind the angle of the incision ensuring that the entire knot of the suture is below the rectus fascia. Subsequent to this, the suture is run in a continuous fashion to reapproximate the fascia until reaching the contralateral rectus abdominus muscle. Subsequently, a second #1 Polysorb™ suture is tied behind the contralateral angle in the same fashion and the remainder of the rectus fascia is reapproximated in a continuous fashion until both sutures are met, whereupon they are tied together.

The remainder of the procedure is completed whereupon the subcutaneous layer is inspected for haemostasis which is achieved using the electrocautery and is reapproximated if >2cm thickness with an absorbable suture. Subsequent to this, the skin is reapproximated using a 3-0 Caprosyn® (polyglytone*6211) suture (Covidien™) in a subcuticular fashion.

As a means of enhancing analgesia, our centre utilises epidural morphine standard as part of their regional anaesthesia for Caesarean Sections, this utilises a single-dose of 0.15mg morphine for spinal regional anaesthesia or a single-dose of 3mg morphine for epidural regional anaesthesia. Upon completion of the procedure, the patient receives one dose of diclofenac 100mg per-rectum and is initiated on oral analgesia as regional anaesthesia wears off. The patient receives a standard analgesia regimen including Tylenol 1g orally every 6 hours, Naproxen 500mg orally every 12 hours, and hydromorphone 1-2mg orally every 4 hours as required for breakthrough

pain. They are subsequently discharged home with a prescription of these three medications for a short course.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

Up to 350 eligible patients will be randomly assigned to one of the three intervention groups in a 1:1 ratio using an Excel-based computer-generated randomisation scheme.

7.2 Blinding

Due to the objectives of the study, treatment group allocation will not be known to investigators, research staff, or patients. The operating surgeon will be informed which method of fascial closure will be undertaken. As such, these individuals will be excluded from collecting outcome data. Upon consenting to proceed with the study, Access to the randomisation code will be strictly controlled and the study blind will be broken on completion of the clinical study and after the study database has been locked.

7.3 Data collection method

Participants will be randomised to one of the three groups and will be provided a participant identification number on the day of their surgical procedure after consenting to proceed with the study. Subsequent to this, a chart review will be used to gather demographic information on participants, including age, gravida and para status, number of previous Caesarean sections, medical and surgical history, medication list, body mass index, and any obstetrical complications during the pregnancy. Participant's e-mails will be collected and saved in a separate document to maintain confidentiality.

Subsequent to this, participants will be e-mailed a link at each given time parameter to fill in their questionnaires which is a modified MD Anderson Brief Pain Inventory as a secure Google Docs Form (post-operative day #1 and 2, and at 2, 6 and 10 weeks post-operatively). As the participant's only identification is their participant identification number, this maintains participant confidentiality.

8 WITHDRAWAL OF SUBJECTS FROM THE STUDY

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Subjects who withdraw from the study will not be replaced.

9 DATA SAFETY MONITORING

Sunnybrook Health Sciences Centre Data Safety Monitoring Board (DSMB) will establish a Data Monitoring Committee (DMC) to review data related to safety and efficacy, to ensure scientific validity and merit of the study, according to Sunnybrook Health Sciences Centre Data Safety Monitoring Board Operations Manual and a DMC Charter to be established for this protocol.

10 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

10.1 Demographic and Baseline Characteristics

The following demographic variables will be collected through a chart review: age, gravida and para status, total number of previous CS, medical history, surgical history, ethnicity, obstetrical history, current obstetrical complications in this pregnancy, medications, height, and weight.

10.2 Statistical Analysis

For our primary outcome measure, we aim to perform statistical analysis using IBM® SPSS® Version. 26 Statistics Software for Windows to perform a two-sided T-test whereby comparing groups directly. Based upon an 80% power at an alpha of 0.05, we anticipate a 15% when comparing group 1 vs 2 and group 1 vs 3, we require a sample size of 255 participants across all three groups.

Specific to our subgroup analysis evaluating primary vs. repeat caesarean section, based upon an 80% power at an alpha of 0.05, we anticipate a 15% difference in comparing these two groups using a two-sided T-test. As a result, we require a sample size of 140 participants across these two groups.

11 DATA COLLECTION, RETENTION AND MONITORING

11.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the research team, but will be identified by a participant identification number.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

11.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

11.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

11.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

11.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation

related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of seven years following completion of the study. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

11.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

11.7 Subject Confidentiality

In order to maintain subject confidentiality, only the participant identification number will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

12 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

12.1 Protocol Amendments

Any amendment to the protocol will be written by the research team. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified.

12.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality

will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted to the Research Team prior to initiation of this study. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

12.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA

authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

12.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

12.5 Investigator Responsibilities

By being involved in this study, the Investigators, as part of the Research Team, agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others.
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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APPENDIX A: Informed Consent Form

Sunnybrook
HEALTH SCIENCES CENTRE
2075 Bayview Avenue, Toronto, M4N 3M5

Informed Consent Form

Study form for: Evaluation of the impact of fascial closure technique on post-operative pain in patients undergoing Pfannenstiel incision for Caesarean Section: A Randomised Trial

This informed consent form is for patients undergoing elective Caesarean sections at Sunnybrook Health Sciences Centre who we are inviting to praticipate in our research trial, titled "Evaluation of fascial closure on post-operative pain in patients undergoing Pfannensteil incision for Caesarean section: A Randomised Trial."

Principle Investigator: Dr. Richard Pittini
Organization: Sunnybrook Health Sciences Centre – DAN Women & Babies Unit

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the study with you)**
- **Certificate of Consent (for signatures if you choose to participate)**

You will be given a copy of the full Informed Consent Form

Part I: Information Sheet

Introduction
Lower Segment Caesarean Sections (LSCS) are the most common surgical procedure performed worldwide. Even in Canada, over 100,000 babies are delivered annually via C-section for a variety of reasons. During this procedure, the layers of tissue are divided to allow for safe delivery of the baby. One layer, the fascia, plays an integral role in ensuring the contents of the abdominal cavity remain in place. The fascia is the layer sitting above your rectus muscles (the "six pack" muscles of your abdomen). This layer is secured during the completion of the surgical procedure to minimise complications. While this layer plays an integral role in ensuring the integrity of the abdominal wall, the most effective method by which this layer is closed has not been studied as it relates to post-operative pain.

Purpose of the Research
The purpose of this study is to evaluate three commonly used methods of fascial closure and their impact on post-operative pain in patients undergoing a lower segment Caesarean section. Currently, no evidence exists with regards to the method by which the fascial layer is closed, and surgeons currently close this layer based on their training. We hope to determine if there is any difference in post-operative pain depending on the method by which the fascia is closed.

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Type of Research Intervention
This study involves comparing three established methods of closure of the fascia. You will be randomised into one of three groups and will be asked to fill in a pain questionnaire after your surgery.

Participant Selection
We are inviting all women who are undergoing an elective Caesarean section at Sunnybrook Health Sciences Centre to participate in this study evaluating three different methods of fascial closure and its effect on post-operative pain.

Voluntary Participation
Your participation in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services and care you receive at Sunnybrook Health Sciences Centre will continue and nothing will change. If you choose not to participate in this research project, you will be offered the care that is routinely offered by your surgeon for your Caesarean section. You may change your mind later and stop participating even if you agreed earlier without any penalties.

Procedure and Protocol
During your surgery, your surgeon will be informed which method of closure of the fascia they will undertake during the procedure. The three methods are described below:

1) Your fascia is closed with one suture which is run across the incision and tied at each edge of the incision, with both knots tied above the fascia.
2) Your fascia is closed with two sutures of the same material which are tied at each edge of the incision, with both knots tied above the fascia, and are then tied to one another in the middle of the incision.
3) Your fascia is closed with two sutures of the same material which are tied at each edge of the incision, with both knots being tied below the fascia, and are then tied to one another in the middle of the incision.

After your procedure, you will be asked to fill in a questionnaire 24 hours after your surgery and on the day of your discharge. The link will be e-mailed to you so that you can fill in the questionnaire. Subsequent to this, a link will be e-mailed to you 2 weeks, 6 weeks, and 10 weeks after your surgery asking you to fill in your questionnaire. Once you have completed the questionnaires, your participation in the study will have been completed.

Duration
Your participation in this study will take place over a period of 10 weeks after your surgery. You will be asked to fill in a questionnaire while you are an inpatient at the hospital, on the day of your discharge, at 2 weeks, 6 weeks, and 10 weeks after your surgery. The entirety of the questionnaire should take approximately 10 minutes each time you fill in the questionnaire.

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Risks
The risks of participating in this study are the same risks as explained to you by your surgeon. There are no additional risks associated with taking part in this study. All methods of intervention for this study are safely used during a Caesarean section by surgeons in this hospital.

Benefits
Your participation in this study may not be of any benefit for you, but is likely to help us find the answer to the research question. The benefits of this study will help to ascertain whether specific surgical techniques will be more effective in minimising post-operative pain for women undergoing lower segment Caesarean sections.

Reimbursements
There are no reimbursements for this study. You will not receive any money or gifts to take part in this study.

Confidentiality
The information that we collect from this study will be kept confidential. Information about you that will be collected during this study will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name, which you will be provided. Only the researchers will know what your number is and this information will not be accessible by anyone other than the members of the research team.

Sharing the Results
The knowledge we get from this research study will be shared with other medical professionals through scientific meetings and publication. Confidential information will not be shared. If you wish to have a meeting discussing the results, please contact Dr. Sandeep Sandhu via e-mail and this can be organised.

Right to Refuse or Withdraw
Your participation in this study is entirely voluntary. If you do not wish to be involved in this study or choose to withdraw from this study prior to it's completion, your care will not be impacted in any way. You will receive the same standard of care provided to all women undergoing a Caesarean section. Your care will not be affected in any way.

Who to Contact
If you have any questions, you can ask them now, or later, through the following contacts:

Dr. Sandeep Sandhu, Study Researcher: sandeepsingh.sandhu@sunnybrook.ca
Dr. Richard Pittini, Study Researcher: Richard.pittini@sunnybrook.ca

This proposal has been reviewed and approved by the Sunnybrook Health Sciences Centre Research Ethics Board and the DAN Women & Babies Unit Research Ethics Committee, which are committees whose task it is to make sure that research participants are protected from harm.

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Part II: Certificate of Consent

I have been invited to participate in research about fascial closure during Caesarean section and its association with post-operative pain.

(This section is mandatory)
I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print name of Participant: _____

Signature of Participant: _____

Date: _____
Day / Month / Year

If illiterate[1]

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of Witness: _____

Signature of Witness: _____

Date: _____
Day / Month / Year

Thumb Print of Participant: ☐

Please provide an e-mail address below. This will allow us to send you all pertinent information for the questionnaire and provide you with your participant ID. This information will be strictly confidential:

E-mail: _____

1. A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well

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Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Participant understands the reason for this research study.
2. Participant understands their role in this research study.
3. Participant understands the reason for follow up as it pertains to this study using the questionnaire tool.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

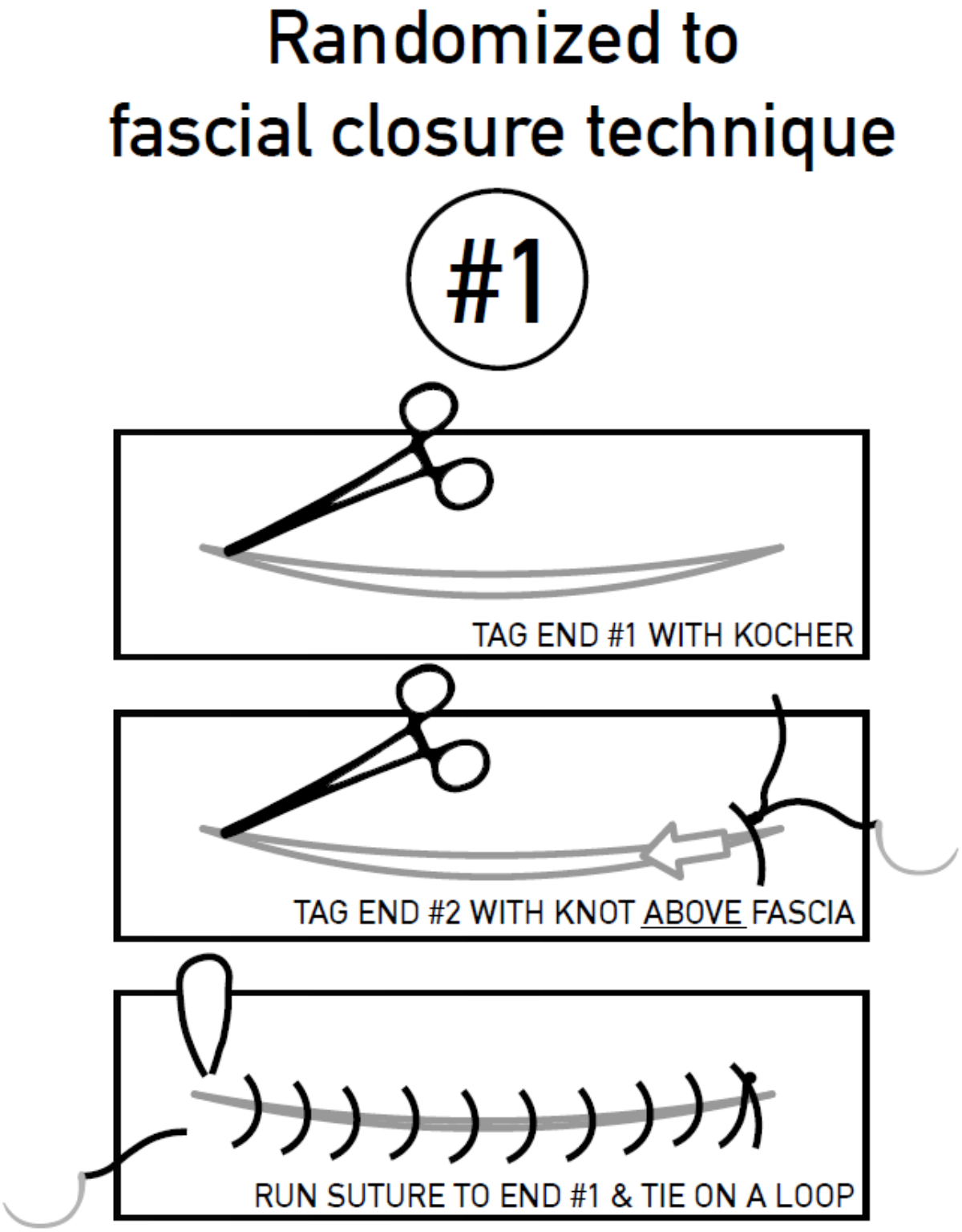
A copy of this ICF has been provided to the participant.

Print name of person taking the consent: _____

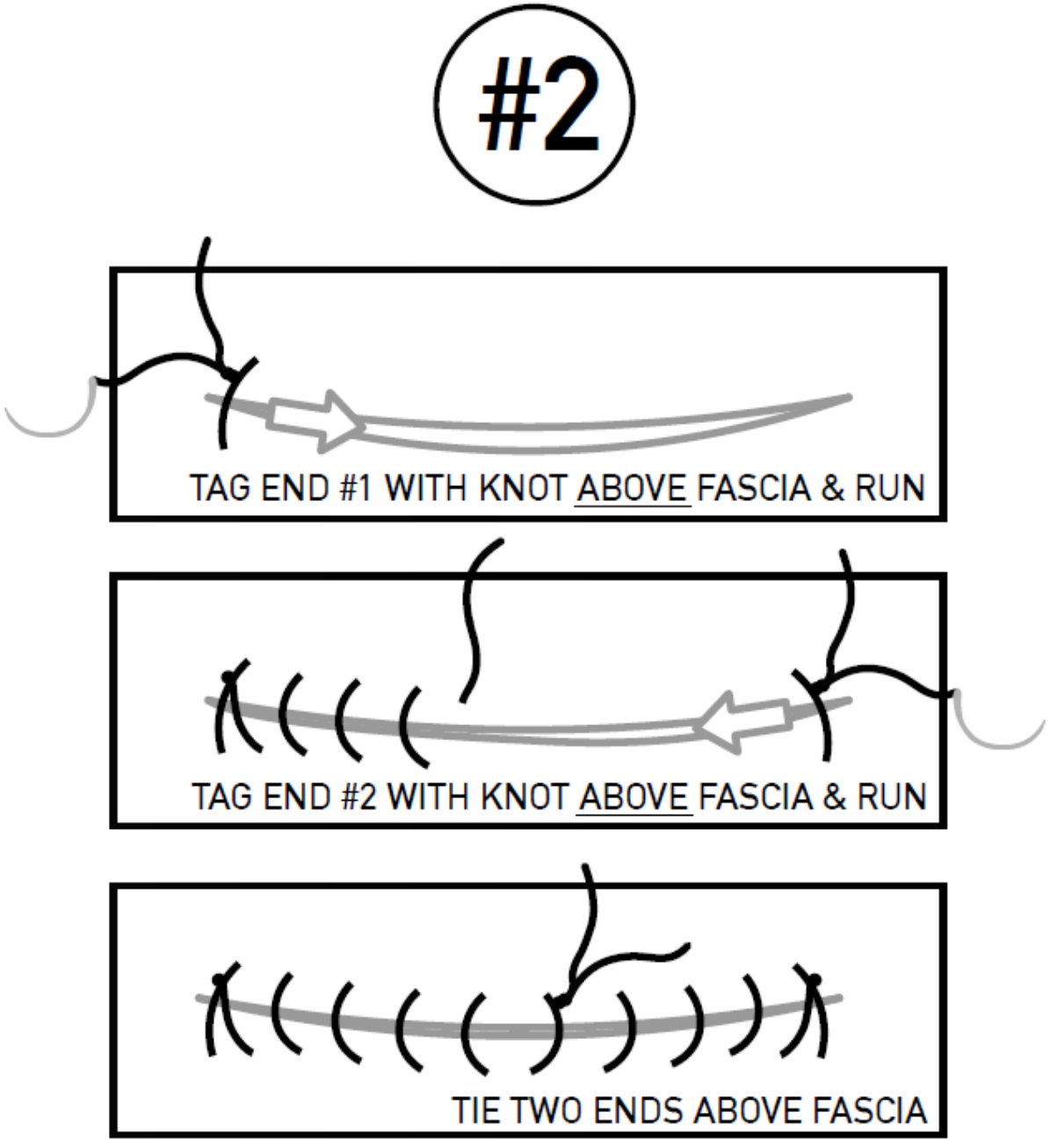
Signature of person taking the consent: _____

Date: _____
Day / Month / Year

APPENDIX B: Figures Showing Methods of Fascial Closure



Randomized to fascial closure technique



Fascial closure study, 2020 PI: Dr. Pittini

Randomized to fascial closure technique

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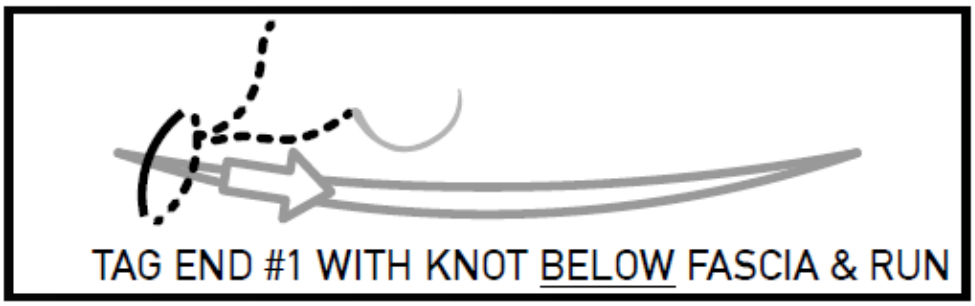
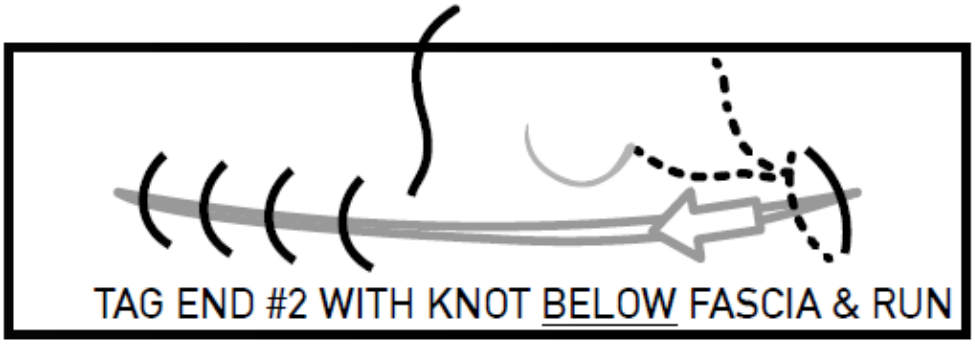
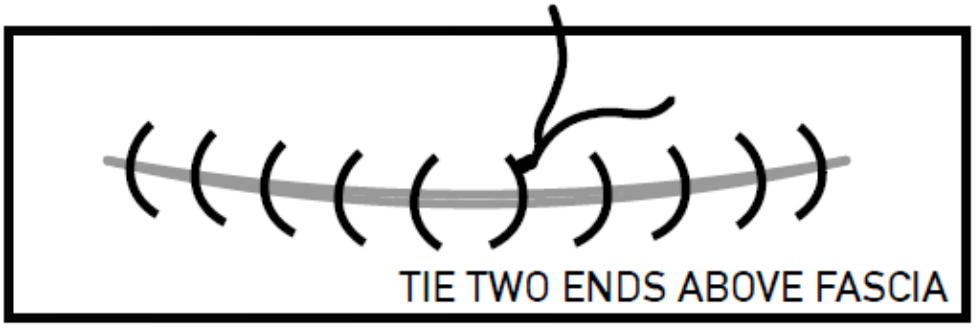






Fascial closure study, 2020 PI: Dr. Pittini

APPENDIX C: Pain Survey Questionnaire

Fascial Closure – Follow-up Study Questionnaire:

Your personal ID: _____

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

□ Yes
□ No

Did you take pain medication in the last 7 days?

□ Yes
□ No

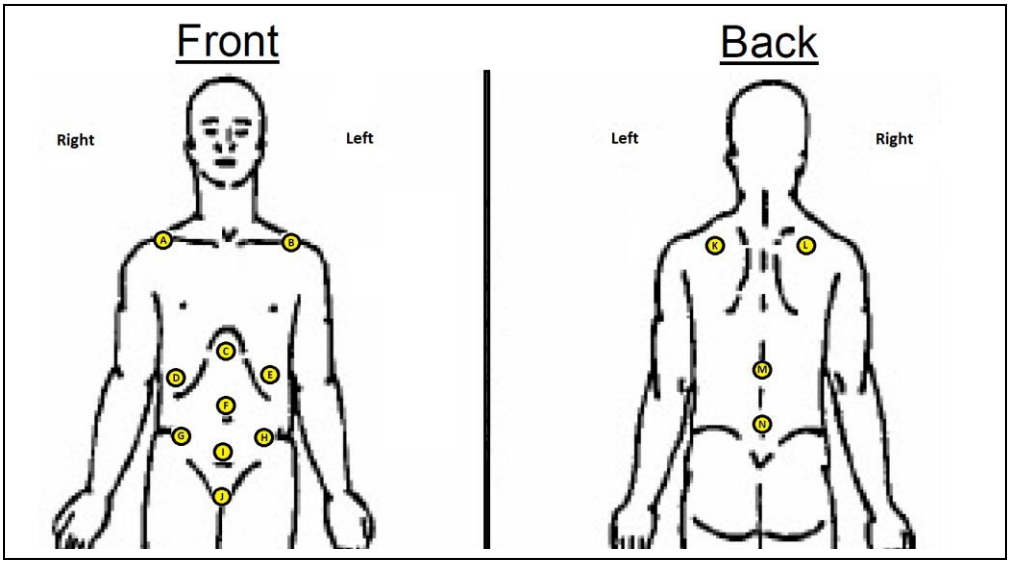
I feel I have some form of pain now that requires medication each and every day.

□ Yes
□ No

If your answers to the above 3 questions were all "No", please stop here and go to the end of the questionnaire and please press "Submit". If any of the above 3 answers were "Yes", please continue.

On the diagram below, please identify the area that hurts the most.

□ A
□ B
□ C
□ D
□ E
□ F
□ G
□ H
□ I
□ J
□ K
□ L
□ M
□ N



Where would you identify this pain?

□ Superficial (closer to the skin)
□ Deep

Please rate the number that describes your pain level at its WORST in the last 24 hours

0 1 2 3 4 5 6 7 8 9 10

No Pin □ □ □ □ □ □ □ □ □ □ □ Worst pain you can imagine

Please rate the number that describes your pain level at its LEAST in the last 24 hours.

	0	1	2	3	4	5	6	7	8	9	10	
No Pin	□	□	□	□	□	□	□	□	□	□	□	Worst pain you can imagine

Please rate the number that describes your pain level on AVERAGE.

	0	1	2	3	4	5	6	7	8	9	10	
No Pin	□	□	□	□	□	□	□	□	□	□	□	Worst pain you can imagine

Please rate the number that describes your pain level RIGHT NOW.

	0	1	2	3	4	5	6	7	8	9	10	
No Pin	□	□	□	□	□	□	□	□	□	□	□	Worst pain you can imagine

What kind of things make your pain feel better? (i.e. heat, medicine, rest, massage)?

_____

What kinds of things make your pain worse (i.e. walking, standing, lifting)?

_____

What treatments or medications are you receiving for pain?

_____

In the last 24 hours, how much relief have pain treatments or medications provided? Please identify the percentage that shows how much relief you have received.

	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
No Relief	□	□	□	□	□	□	□	□	□	□	□	Complete relief

For each of the following words, please check all adjectives that apply to your pain.

□ Aching
□ Burning
□ Dull
□ Exhausting
□ Gnawing
□ Miserable
□ Nagging
□ Numb
□ Penetrating
□ Pulling
□ Sharp
□ Shocking
□ Shooting
□ Stabbing
□ Tender

□ Throbbing
□ Tiring
□ Unbearable

In the last 24 hours, how much has your pain interfered with your general activity?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

In the last 24 hours, how much has your pain interfered with your mood?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

In the last 24 hours, how much has your pain interfered with your walking ability?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

In the last 24 hours, how much has your pain interfered with your normal work (includes both work outside the home and housework)?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

In the last 24 hours, how much has your pain interfered with your relations with other people?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

In the last 24 hours, how much has your pain interfered with your sleep?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

In the last 24 hours, how much has your pain interfered with your enjoyment of life?

	0	1	2	3	4	5	6	7	8	9	10	
Does not interfere	□	□	□	□	□	□	□	□	□	□	□	Completely interferes

I prefer to take my pain medication:
□ On a regular basis
□ Only when necessary
□ Do not take pain medicine

I take my pain medicine (in a 24 hour period):
□ Not every day
□ 1 to 2 times per day
□ 3 to 4 times per day
□ 5 to 6 times per day
□ more than 6 times per day

Do you feel you need a stronger type of pain medication?

□ Yes
□ No
□ Uncertain

Other methods I use to relieve my pain include: (Please check all that apply)

□ Warm compresses
□ Cold compresses
□ Relaxation techniques
□ Distraction
□ Biofeedback
□ Hypnosis
□ Other: _____