ENDOMETRIOSIS DEEP DYSPAREUNIA AND CENTRAL SENSITIZATION

NCT: 03216330

PRINCIPAL INVESTIGATOR

Dr. Paul Yong, MD, PhD, FRCSC
Department of Obstetrics & Gynecology, University of British Columbia

CO-INVESTIGATORS

Dr. Mohamed Bedaiwy, MD, PhD, FACOG, FRCSC
Professor, Department of Obstetrics & Gynecology, University of British Columbia

Dr. Christina Williams, MD, FRCSC
Clinical Assistant Professor, Department of Obstetrics & Gynecology, University of British Columbia

Dr. Catherine Allaire, MD, FRCSC
Clinical Associate Professor, Department of Obstetrics & Gynecology, University of British Columbia

Natasha Orr, BSc
Graduate Student, Department of Obstetrics & Gynecology, University of British Columbia

BACKGROUND LITERATURE

Endometriosis results from the presence of endometrial cells growing abnormally outside the uterus and affects approximately 10% of reproductive-aged females[1,2]. Endometriosis can be associated with various types of pain such as: dysmenorrhea (painful cramps with menses), deep dyspareunia (pelvic pain with deep intercourse), dyschezia (painful bowel movements) and chronic pelvic pain. Few studies have explored the association between endometriosis and deep dyspareunia resulting in a limited understanding of how to treat deep dyspareunia. Deep dyspareunia is defined as pelvic pain with deep sexual intercourse and occurs in 50% of women with endometriosis at some time in their sexual lives[3]. Deep dyspareunia has been shown to lower or cease intercourse, thus lowering self-esteem and resulting in negative effects on sexual functioning and interpersonal relationships[3,4].

A potential contributor to deep dyspareunia in women with endometriosis that is largely under-researched is the concept of central sensitization. Central sensitization is an amplification of nociceptive signaling that may result from prolonged pain causing sensitization of the dorsal horn neurons, which results in hyperalgesia (increased response to pain) and allodynia (response to pain when there normally

would not be)[5,6]. A recent study, comparing cross-sectional data from suspected or surgically diagnosed endometriosis patients, suggested that bladder and pelvic floor tenderness may be markers of central sensitization[7]. However, the linkage between the indirect markers of central sensitization and the presence of central sensitization requires confirmation. This link can be assessed through validated quantitative sensory testing (QST)[8]. Likewise, the association between central sensitization and deep dyspareunia may also be confirmed through QST. QST is an objective measurement tool to determine the presence and/or degree of sensory disturbances, by detecting the alterations in nociceptive pathways[9]. For example, a low pain-pressure threshold (i.e., increased pain sensation) at healthy unaffected areas, as measured by QST, indicates central sensitization.

RESEARCH OBJECTIVES

Purpose: To determine if there is an association between bladder and pelvic floor tenderness, and measures of central sensitization, and if measures of central sensitization are associated with deep dyspareunia.

Research Question: Does an increased severity of deep dyspareunia result in a decreased pain-pressure threshold (measure of central sensitization)?

Objectives:

Primary Objective:

1) Examine the correlation between central sensitization and severity of deep dyspareunia.

Secondary Objectives:

1) Examine the correlation between central sensitization and severity of non-sexual pains and Endometriosis Health Profile (EHP-30) scores.
2) Examine the correlation between central sensitization and tenderness of the bladder and pelvic floor (determined by physician on physical exam).
3) Examine variations in severity of deep dyspareunia in women with the same disease state of endometriosis.

Research Hypothesizes:

Primary Hypothesis: Central sensitization (measured by pain-pressure threshold) is associated with an increased severity of deep dyspareunia, as well as a tenderness of the bladder and pelvic floor, in women with endometriosis.

Secondary Hypothesis: Women with endometriosis will have a great central sensitization (indicated by a lower pain-pressure threshold) than women without endometriosis.

Outcome: Central sensitization (lower pain-pressure threshold) will be strongly and positively correlated with the severity of deep dyspareunia, and will also be associated with bladder and pelvic floor tenderness.

RESEARCH DESIGN/PROCEDURES

Setting

The Pelvic Pain and Endometriosis program at the BC Women's Health Centre uses an interdisciplinary approach to managing pain, including: physiotherapy for bladder and pelvic floor, surgical intervention, pain education and medical management. This program addresses multiple factors influencing pain through multiple approaches, as opposed to the traditional approach of surgical removal of the endometriosis to resolve the pain alone.

Design

This study is a longitudinal, prospective cohort study, involving cases and controls. The analyses will be carried out within cases, while the controls are primarily used for troubleshooting and optimization of the QST. We will collect data prior to the test date (QST appointment) and data on the test date (for cases and controls), as well as six weeks of daily survey completion after the test date, for cases only.

Primary Outcome: Severity of deep dyspareunia

Secondary Outcomes: Severity of superficial dyspareunia, severity of non-sexual pains, sexual quality of life (EHP-30)

Main Independent Variables: Central sensitization (measured by pain-pressure threshold (PPT) determined through QST)

Study Population: The case population includes women who have consented to the Data Registry (H16-00264) and who are new or re-referred to the BC Women's Health Centre for Pelvic Pain and Endometriosis, and who have, regardless of the severity of deep dyspareunia, either: 1) previous surgical diagnosis of endometriosis or 2) current ovarian endometrioma cyst or 3) current endometriosis nodule.

Sample Size: 126 cases and 50 controls. Due to the nature of the testing in this study and the fact that participants may not benefit directly from participating in this study, it is difficult to estimate the percentage of individuals who will take part in this study. However, we estimate that it will take approximately 6 months to recruit our desired sample size of 176 participants, and we will be assessing the recruitment rate throughout the study period. At the Centre, we see approximately 300 patients meeting the criteria for this study per year.

Inclusion Criteria:

Case:

- Consented to participate in the Data Registry (H16-00264) prior to their physician appointment at the BC Women's Health Centre.
- New or re-referred to the BC Women's Health Centre for Pelvic Pain and Endometriosis.
- Endometriosis (previously surgically diagnosed, or current endometrioma, or current nodule)

- Willing and committed to indicating pain scores and menstrual data on a REDCap survey every day for 6 weeks after the test date.

- At least 18 years old

Control:

- Reproductive aged female with no suspected or diagnosed endometriosis.

- Have not experienced any sexual pain scores over 4/10 on a 11-point numeric rating scale, as determined on an online questionnaire prior to test day.

- At least 18 years old

Exclusion Criteria:

Case and Control:

- Fibromyalgia.

- Severe and enduring psychological illness(es) affecting cognition (e.g., bipolar disorder, schizophrenia etc.).

- Currently pregnant or breastfeeding.

- Have a peripheral or central neurological disorder.

- Have diabetes mellitus or neuropathic pain.

- Do not speak English.*

- Have had previous physical trauma (ex. Surgery) to the test site(s) (deltoid muscle in the shoulder, and first dorsal interosseous muscle).

*Patients who do not speak English will be excluded to maintain the safety and wellbeing of the patient, as not understanding the test and process may put the patient in harm, as well as maintaining the validity of the results. We do not have research funding for a translator.

<u>Recruitment and Data Collection prior to Test date:</u>

Case:

- At the end of their appointment with one of the endometriosis specialists at the BC Women's Health Centre for Pelvic Pain and Endometriosis, the physician will ask the patient if they are interested in learning more about this research study (if the physician deems them acceptable to be included based on screening of inclusion and exclusion criteria). The physician will provide the patient a copy of the consent form to read at home and will ask the patient if Natasha Orr or her delegate can call them in the next couple of days. Physicians will emphasize that participation is optional and does not influence their health care.

- A poster introducing the study will also be available in the clinic waiting rooms.

- Potential participants will be encouraged, if they feel comfortable doing so, to discuss the consent form with family, friends, and/or their physician. The potential case participants will be given a minimum of 24 hours to review the consent form before being contacted by Natasha Orr or her delegate.

- Heather Noga will collect the physician forms and will confirm that the interested potential case participants consented to the data registry. Heather Noga will only give Natasha Orr the contact information of the potential case participants that consented to the data registry. During the first phone call, Natasha Orr or her delegate will ask if the potential case participant is interested in participating in the study, and will explain the study and consent process, if they wish. During this phone conversation, Natasha Orr will remind the potential case participant that they have consented to the data registry, and consent to this study allows us access to analyze their data registry data. Verbal consent will be given if the potential case participant would like to participate, and a test appointment will be booked. Natasha Orr or her delegate will log the participant into the test computer during the test day so that they can complete the test day questionnaire online.

- Case participants will sign the consent form in-person at the beginning of the test day appointment.

- Note that the case participants do not need to complete the Data Registry questionnaire again, since we will be linking to their previously completed Data Registry questionnaires done before their physician appointment.

- Participants will be instructed not to take analgesics within 24 hours before the scheduled test, nor to take opioids within 2 weeks before the scheduled test, nor to consume alcohol within 24 hours prior to scheduled test time. The participants will also be told to wear comfortable clothing with easy access to their shoulder for the scheduled appointment.

Control:

- Recruitment of the control group will be done by poster advertisement at the BC Women's Hospital. If they are interested in the study, potential participants will be asked to contact Natasha Orr (contact information on poster) to learn more about the study.

- In addition to a poster advertisement, the research assistant will circulate an invitation (via. email/social media) to an in-person information session open to all potential control participants who may be interested in the study.

- In-person information sessions and poster advertisement may also be done at the BC Children's Hospital, the BC Children's Hospital Research Institute (BCCHRI), and the University of British Columbia.

- An in-person information session includes: a short presentation about the research study and what is required of the control participants, and contact information will be left for the potential control participants if they would like more information/if they would like to participate.

- Recruitment of control participants may also be done through institutional research newsletters.

- Natasha Orr or her delegate will mention to participants in the study that their friends and family are welcome to contact us if they would like to participate, and will provide the participant a copy of the poster. This will happen at the final interaction between the participant and the research so they do not feel pressure.

- In addition, we will recruit via electronic forms of communication (e.g. institutional listservs (CRC net for the BC Children's Hospital Research Institution) or research/student groups).

- Natasha Orr or her delegate will provide the potential control participant with a copy of the consent form (in person or by email). Each potential control participant will be advised to carefully read the consent form, and to contact Natasha Orr with any questions about the information contained in the consent form. Potential participants will be encouraged, if they feel comfortable doing so, to discuss the consent form with family, friends, and/or their physician. The interested control participants will give Natasha Orr or her delegate their contact information via in person or email. They will be given a minimum of 24 hours to review the consent form before being contacted by Natasha Orr or her delegate who will ask if they would like to take part in the study.

- If the control participant expresses interest in the study after reading the consent form, Natasha Orr or her delegate will send them a link to access the REDCap screening questions indicating sexual and non-sexual pains, age, and history of fibromyalgia (see attachment). Each control subject will be assigned a de-identified unique study ID.

- Criteria will be assessed by screening questions. If the participants are eligible based on the screening questions (18 years or older, pain scores less than 4/10, and no fibromyalgia) then they will be asked if they would like to consent to the study (online consent). This online consent allows access to the data from the screening questions. If they are not eligible, or do not consent to the study their screening questions will not be analyzed. If the control participant consents online they will be asked to complete additional questions on REDCap (height, weight, etc. See attached).

- Natasha Orr will receive an email from REDCap once the control participant has consented online, and will contact the participant to book a test day appointment.

- If the control participant had not completed the pre-test questionnaire after one week, they will be sent an email reminder.

- On the test day, the consent participants will sign the same consent form in-person to consent to the testing procedures.

- Participants will be instructed not to take analgesics within 24 hours before the scheduled test, nor to take opioids within 2 weeks before the scheduled test, nor to consume alcohol within 24 hours prior to scheduled test time. The participants will also be told to wear comfortable clothing with easy access to their shoulder for the scheduled appointment.

<u>Procedures for Data Collection (on Test day)</u>

Questionnaire:

Case and Control:

- Data will be collected during a scheduled appointment with Natasha Orr or her delegate. The research visit will take approximately one hour of the participant's time (not including travel time to and from the site). The visit will take place in a BC Women's Health Centre private room (4th floor of the Shaughnessy building at the BC Women's Hospital). Data collected will include an online questionnaire containing: today's date, score of sexual and non-sexual pains, first day of last menstrual period, any changes in medication since their last visit to BC Women's Health Centre, current hormonal suppression, date of last physician appointment, menstrual cycle data, last time they have had sexual intercourse and how many times have they had sexual intercourse in the last one month. The pelvic pain questions asked on this online questionnaire are modified from the Brief Pain Inventory Short Form. This questionnaire will be filled out on REDCap online using a desktop computer in the room.

- The testing room will be maintained at a temperature between 20 and 25 degrees Celsius, with no fans or open windows (may use a white noise machine), and no stressful stimuli (e.g., no loud noises or blinking lights).

- As the participant completes the online questionnaire, Natasha Orr or her delegate will set up the Algometer and calibrate the force sensing resistor (FSR). Natasha Orr or her delegate will answer any questions.

Quantitative Sensory Testing (QST):

Case and Control:

- After the questionnaire has been completed, the participants will undergo QST to measure their pressure-pain threshold (PPT), the point where the sensation of pressure has changed to the sensation of pain (or first report of discomfort). This procedure will take approximately 30 minutes. Before testing begins, it will be made clear that the participants can withdraw from the study even during the procedure if they find it too uncomfortable.

- The PPT data will be written down on a paper copy with the unique study ID, and entered into an encrypted excel file.

- The testing room will be at a temperature between 20 and 25 degrees Celsius, with no fans or open windows, and no stressful stimuli (e.g., no loud noises or blinking lights). The participants will be sitting on a chair when QST occurs and before testing they will be asked if they are comfortable.

- QST, to measure PPT, will be done using an Electronic Thimble Algometer (purchased from the University of North Carolina). The Electronic Thimble Algometer consists of a calibration load cell and a force sensing resistor (FSR), as well as an amplifier which "reads" the force from the resistor and transfers the data to the connected computer (a laptop). The calibration load cell will be calibrated using 2 weights (0kg and 0.5kg) (Fisher Scientific, Cat #:S01369), as per the manufacturers recommendations. The FSR will then be calibrated on the load cell. The calibrations will ensure the accuracy and reliability of the measurements. Four test sites will be measured: left deltoid muscle, right deltoid muscle, and left first dorsal interosseous muscle and right first dorsal interosseous muscle. All test sites will be measured twice; therefore, the PPT will be measured eight times. The test sites will be measured bilaterally and duplicated to obtain an average value. The order of the test sites will be measured randomly (done automatically by

the Electronic Thimble Algometer). The investigator will describe the process of this test to the participant, following this script:

> "*This instrument is called the Electronic Thimble Algometer and will be used today to measure your pain pressure threshold. The pain pressure threshold is when the sensation of pressure changes to the first sensation of pain. During this test I will place this part of the instrument, called the force sensing resistor, on the end of my index finger and will apply a constant pressure to your right shoulder, left shoulder, right first dorsal interosseous muscle and yourleft first dorsal interosseous muscle. The pain-pressure threshold measurement from these four sites will be duplicated. The order of the test sites will be determined randomly. I will constantly apply pressure to the test site until you click on the mouse indicating that the sensation of pressure has changed to the sensation of pain. Please click the mouse at your first sensation of pain. There will be a thirty second break between each test site, and then a two minute break before duplicating the test. You will hear the prompt for the next test site after each of the breaks. If at any time you are no longer comfortable or change your mind about participating, please let me know. I will then stop the testing immediately. Do you have any questions before we begin?"*

This script will be read to each participant before the test begins. Any questions or concerns they have will be answered to the best of the investigators ability and/or addressed before they willingly partake in this test.

- The participants will be blinded to the computer screen (where the PPT data is shown) to ensure they are not influenced by the data during the QST
- The observation made by this QST is that a lower PPT is suggestive of increased central sensitization.
- After testing the individual will remain in the test room until she feels ready to leave.

Feedback Questionnaire:

Case and Controls:

- After the participant's PPT has been measured, they will be given an anonymous feedback form to assess the procedure mechanisms and specifications, as well as comfort level before, during and after testing. This will allow investigators to adjust any necessary procedure details to create a more comfortable environment/test for future participants.

A mental health recourse sheet will be given to every participant at the end of the appointment. If the participant requires more support than Natasha Orr can provide, the participant will be directed to the clinic nurse. The clinic nurse will triage the participant and provide them with the level of care the participant needs. If it is an emergency situation, 911 will be called.

<u>Procedures for Data Collection (after Test day)</u>

Online Survey:

Cases only:

- After recruitment and signing the consent form, case participants will be asked to record study data daily after their scheduled test date.

- REDCap surveys will be completed for six weeks after the test date, and data will be collected at the end of the six weeks. The data collected on the surveys for this study is shown in Appendix C.

- The data collected (shown in Appendix C), will allow for daily prospective pain scores, rather than retrospective recollections of pain scores.

- All case participants will receive daily notifications to complete the survey. Case participants will be sent one email reminder in the evening if they have not filled out the questionnaire that day. A Mental Health Crisis line number is given on the notifications in case the participant becomes distressed. At the end of the first week of entering the survey data, the participants will receive a phone call, from Natasha Orr or her delegate, to follow up on usage and any troubles or suggestions. Any problems will be addressed by Natasha Orr.

Participants without email addresses will have the opportunity to complete the surveys on a printed out copy (given to them on the appointment day) and mail/bring in-person to the Centre at the end of the 6 weeks. Two weeks after the end of the study (after 6 weeks of survey entry), if the participant who completed their surveys on printed copies have not sent in their data, Natasha Orr or her delegate will call the participant to kindly remind them to mail/bring in the data.

The recruitment and procedures for this study are illustrated in Appendix A (Case) and Appendix B (Controls).

Data Linking:

The Data Registry for Chronic Pelvic Pain and Endometriosis (H16-00264) collects a wide range of data from all consenting patients of the BC Women's Centre for Pelvic Pain and Endometriosis including those who undergo surgery at the clinic. Case participants in this study (Endometriosis deep dyspareunia and central sensitization) are therefore also listed in the Data Registry (they consent to both). This will allow for direct matching. A data access request will be sent to the research coordinator (Heather Noga) to collect the case participant data from the Data Registry. The information provided to the Data Registry research coordinator for data linking includes: unique study ID, MRN, PHN, first and last name, and date of initial visit to BC Women's Health Centre. All the data from the Data Registry is being linked. This data will be placed in an encrypted excel file on the O: drive. The research coordinator will pull the appropriate information and replace the participants Data Registry REDCap ID with the unique study ID for this study and place the file back on the O: drive, where Natasha Orr or her delegate will have access to it. Data for both studies are kept on the BC Women's secure O: drive in separate password protected folders with restricted access to study team members; therefore the data transfer can be undertaken within the PHSA secure network.

Once data linkage is complete the linking spreadsheet sent to the Data Registry research coordinator will be permanently deleted as per UBC policy 85.

Data Transfer:

We have both a PHSA networked computer in our lab (where data is stored) and UBC networked computers in our lab and with our statistician (both at BC Women's Hospital).

In order to analyze the data using sophisticated statistical analysis software it is necessary to transfer coded data temporarily from the PHSA networked computer to a UBC networked computer to complete the analysis. The data storage described above will not change. Identifiable information will never be transferred from the secure PHSA network.

A) Coded information only. No identifying information will be transferred.

B) The data will remain within the study team.

C) The data will be transferred for use on a UBC networked computer for data analysis but the data will not be stored on the UBC computer. All data will continue to be stored on the secure PHSA network.

D) Data will be transferred to an encrypted/password protected USB stick for use on a UBC networked computer temporarily for analysis. The data will always be returned to the PHSA network for storage. The UBC computers are housed in the same physical location as the PHSA computers.

DATA ANALYSIS

The data collected from the 30 case participants was used to execute a power analysis to determine the total sample size required for the study. With power=0.80 and α=0.05 two tailed, a sample size of 126 case participants was needed.

For the cases, statistical analysis following collection of the data will be done using a Spearman Correlation determine if there is significant association between PPT and the primary outcome (deep dyspareunia) and secondary outcomes (e.g. non-sexual pain). Mann-Whitney association may be done for the bladder and pelvic floor variables to determine if they are significantly associated with PPT. Multiple Variable Regression may be done using variables significantly associated to determine if they are independently associated, independent of possible confounders. Comparison of PPT between cases and controls will also be done, but the main reason for the controls is for troubleshooting of the QST.

ETHICAL CONSIDERATIONS

Risk to participants: By participating in this study the participants will experience pain or discomfort due to the measurement of PPT. However, the test inflicts the least amount of pain, as the test is stopped immediately once the participant feels any discomfort. Additional risks associated with completing very personal questions and undergoing QST due to the case participant's possible history of chronic pain includes: psychological, emotional or physical discomfort. If any additional risks are discovered, these risks will be disclosed immediately and new consent forms will be created and sent to participants. If any adverse reactions were to occur, the participant will be triaged by the clinic nurse at the BC Women's Health Centre, and assessed by a physician if required. Another risk to participants is accidental release of data. All precautions are being taken to assure that this does not occur (e.g. limited access, limited data transfer, de-identifying the data, etc.).

Risk to investigators: There are no known risks to investigators. Any risks that are discovered will be disclosed immediately to the study PI.

Benefit: There are no direct benefits to the health care of the participants. Our Centre sends regular newsletter to participants, to update them on research findings.

Informed Consent Process: The patients will be given a minimum of 24 hours to decide whether or not they want to participate. Natasha Orr or her delegate will explain the consent form in detail to the patients and will answer any questions they may have. If deciding to participate, the patients will consent to the study in-person, as well as on REDCap for the control participants. .

Privacy and Confidentiality: As outlined in the procedures, each participant record on REDCap is assigned a unique study ID number that can only be decrypted by a linking excel file separately stored on the PHSA restricted access secure O: drive. This linking spreadsheet is encrypted and kept in a folder that can only be accessed by select members of the clinical and research team. Care will be taken that unique study IDs and identifiers will not appear together anywhere other than the master file.

Within REDCap, each record contains an embedded email for the purpose of sending automated invitations with a link to initial pre-visit questionnaire (controls only),consent form (controls only) and post-appointment day daily surveys (cases only).

No participant data will be stored on the test laptop. The PPT data will be written down on a paper copy with the participant's unique study ID at the top to link them to their REDCap data. The paper copy will be entered into an encrypted file on a PHSA secure computer. All paper data will be placed in a confidential file box and shredded as per hospital policy. If needed, computer files will be deleted according to UBC policy 85.

The data from the survey can be viewed by Natasha Orr or her delegate via REDCap; therefore, there is no risk of disclosure of information by unsecured email servers.

All researchers in this study have been trained in the proper protocol for privacy and confidentiality, including completion of the Tri-Council Policy Statement: Ethical conduct for Research Involving Humans (TCPS-2 CORE) and a Privacy and Confidentiality course provided by PHSA.

DATA STORAGE/ DATA HANDLING

The online questionnaires, daily surveys and control consent form will be housed on the Research Electronic Data Capture (REDCap) platform located at the Child and Family Research Institute (CFRI) on the BC Children's and BC Women's Hospital and Health Centre campus.

The actual data for each database is stored on a private, relational MySQL Database at the data center which is located on-site at CFRI. CFRI IT is responsible for creating REDCap database backups and these backups are stored at Iron Mountain Canada, ensuring that all data and backups are stored in Canada. The CFRI Clinical Research Support Unit (CRSU) stores study data in a secure, firewall protected server with only the https ports available to internet. There is a web application server that is the only gate to connect to the Database server, where the information is stored.

The Database Management System uses a web server that employs Secure Socket Layer (SSL) technology for the secure transfer of data between a client computer and the server. The actual data center is a physical secured and protected area. Physical access to this room is extremely limited and is controlled by CFRI IT and security personnel through a process of authorizing and granting access linked to identification cards. A record of access rights is recoded and kept by both the CRFI IT and security personnel. The data center is also patrolled by on-site security personnel, monitored by surveillance cameras, and protected by a fire suppression system.

PPT measurements will be stored in an encrypted file on the O: drive within the PHSA network. Only investigators in this study and delegates will have access to this file. No data will be stored on the test laptop or the UBC computer.

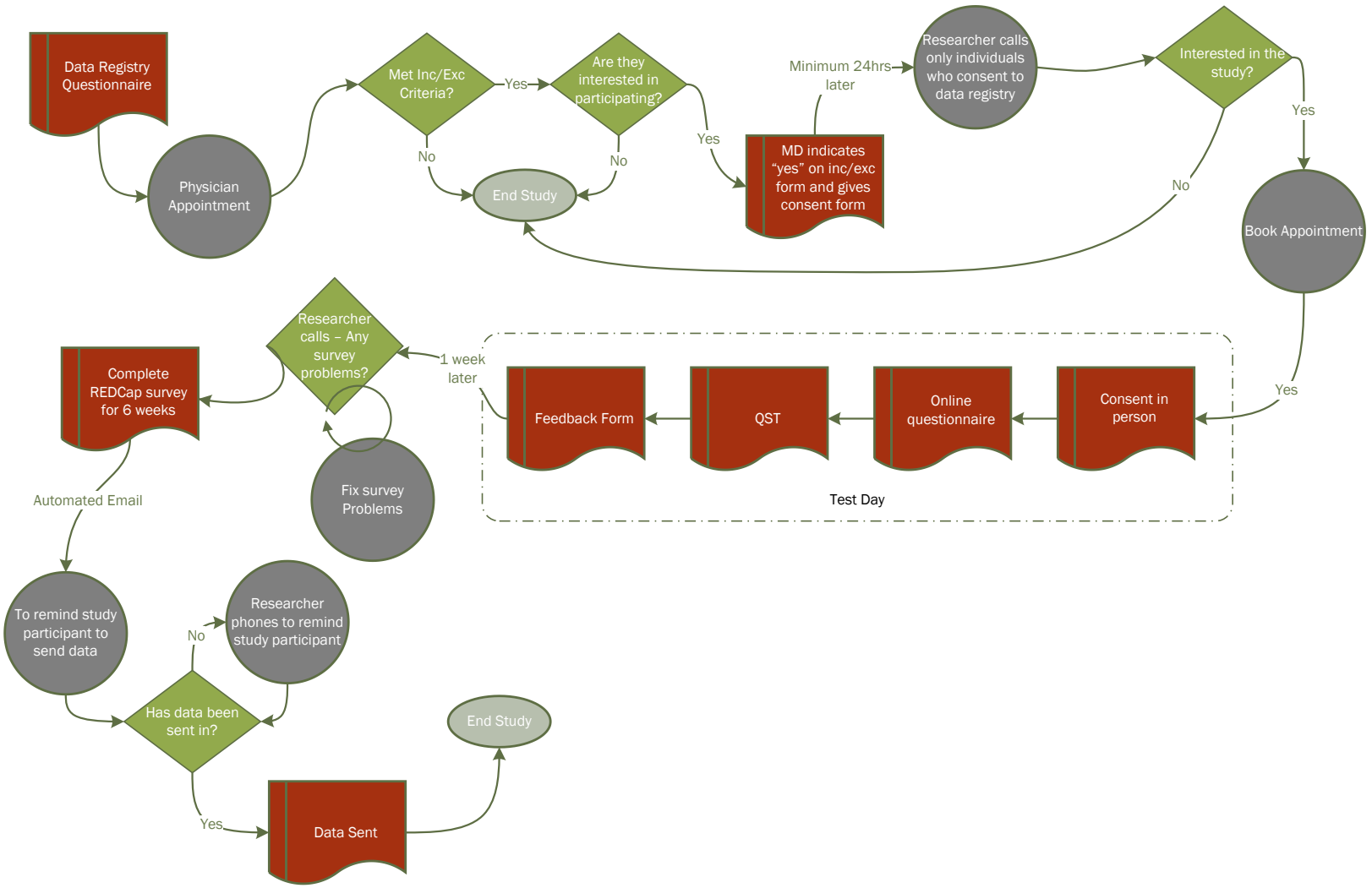
DISSEMINATION OF RESULTS

Results from the study will be published in academic and non-academic journals, presented at conferences or events and made available online (e.g. departmental or individual websites). Participants will be notified of the results of the study through our research newsletter.

REFERENCES

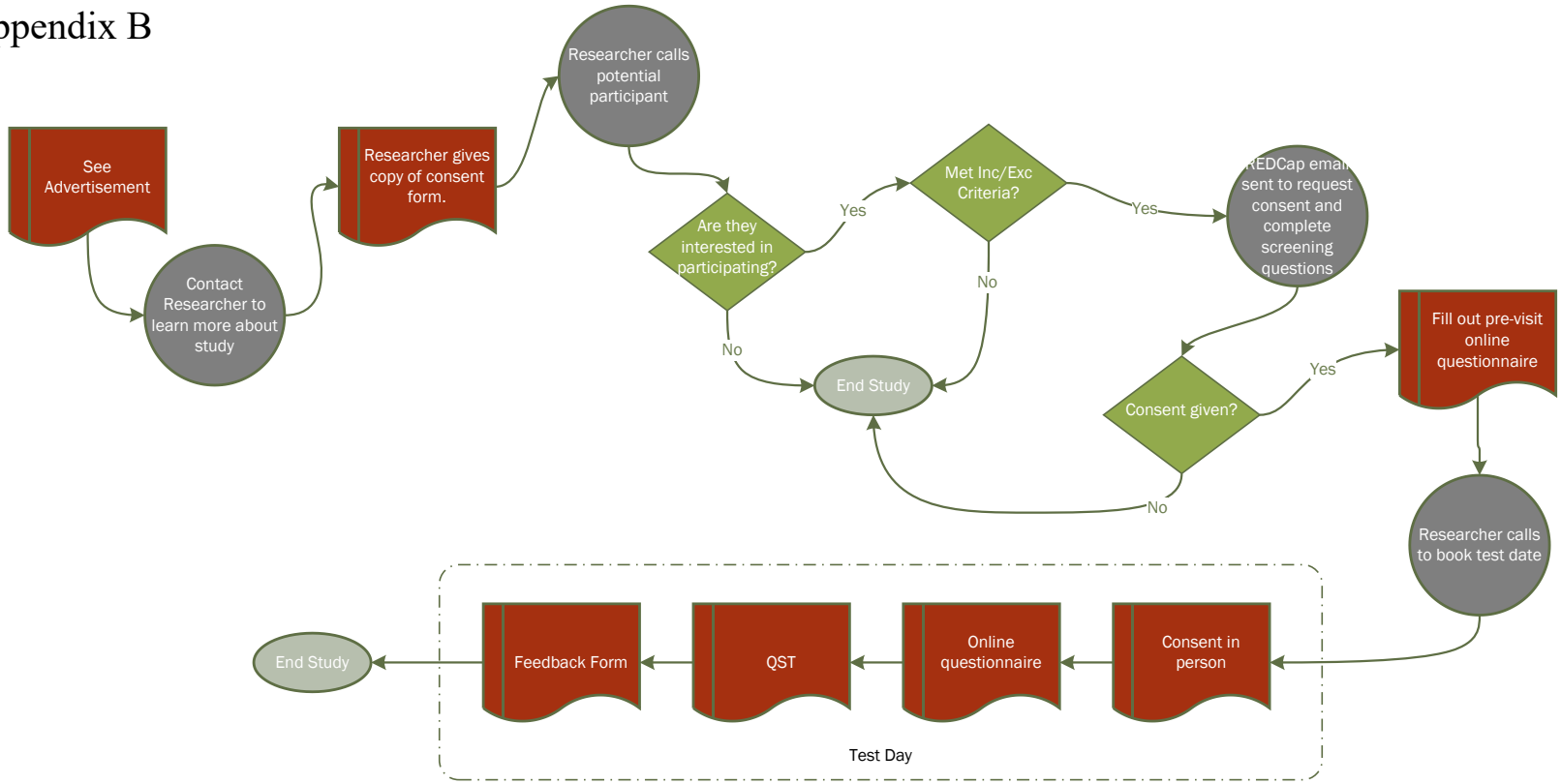
1. Giuliani, M., Cosmi, V., Pierleoni, L., Recine, A., Pieroni, M., Ticino, A., & Simonelli, C. (2016). Quality of life and sexual satisfaction in women suffering from endometriosis: An Italian preliminary study. *Sexologies*, *25*(1), e12-e19.
2. Mendiola, J., Sánchez-Ferrer, M. L., Jiménez-Velázquez, R., Cánovas-López, L., Hernández-Peñalver, A. I., Corbalán-Biyang, S., & Torres-Cantero, A. M. (2016). Endometriomas and deep infiltrating endometriosis in adulthood are strongly associated with anogenital distance, a biomarker for prenatal hormonal environment. *Human Reproduction*, dew163.
3. Denny, E., & Mann, C. H. (2007). Endometriosis-associated dyspareunia: the impact on women's lives. *Journal of Family Planning and Reproductive Health Care*, *33*(3), 189-193.
4. Ferrero, S., Esposito, F., Abbamonte, L. H., Anserini, P., Remorgida, V., & Ragni, N. (2005). Quality of sex life in women with endometriosis and deep dyspareunia. *Fertility and sterility*, *83*(3), 573-579.
5. Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *The Journal of Pain: Official Journal of the American Pain Society*, *10*(9), 895–926
6. Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science*, *288*(5472), 1765-1768.
7. Yong, P. J., Williams, C., Yosef, A., Wong, F., Bedaiwy, M., Lisonkova, S., & Allaire, C. (under review). Etiology of deep dyspareunia in women with endometriosis and pelvic pain. *Human Reproduction*.
8. Reynolds, W. S., Dmochowski, R., Wein, A., & Bruehl, S. (2016). Does central sensitization help explain idiopathic overactive bladder? *Nature Reviews Urology*.
9. Yarnitsky, D. (1997). Quantitative sensory testing. *Muscle & nerve*, *20*(2), 198-204.

Appendix A



Note: Researcher is Natasha Orr or her delegate

Appendix B



Note: Researcher is Natasha Orr or her delegate

Appendix C

Question	**Range of Responses**
Today's Date	
What was your average level of pelvic pain in the last 24 hours?	0= no pain, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10= worst pain imaginable
Have you experienced menstrual bleeding in the last 24 hours?	0= none, 1=spotting, 2= bleeding
In the last 24 hours, how painful was deep penetration during sexual intercourse?	Not applicable (no intercourse), 0= no pain, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10= worst pain imaginable
In the last 24 hours, how painful was initial penetration (entry) during sexual intercourse?	Not applicable (no intercourse), 0= no pain, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10= worst pain imaginable