University of California, San Diego
Consent to Act as a Research Subject

Title: Study of Uterine Prolapse Procedures- Randomized Trial - (Short name: 'SUPeR') Protocol Ver. 2.0

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Co-Investigators: Charles Nager, MD; Michael Albo, MD; Marianna Alperin, MD

Sponsors: Pelvic Floor Disorders Network (PFDN) supported by National Institute of Child Health and Human Development (NICHD), the National Institutes of Health Office of Research on Women's Health and Boston Scientific Corporation

Data Coordinating Center: Research Triangle Institute (RTI)

DESCRIPTION & PURPOSE OF THE STUDY

Dr. Emily Lukacz, her colleagues at UCSD, and members of the Pelvic Floor Disorders Network (PFDN) are conducting this study to compare 2 surgical procedures to repair prolapse of the uterus and vagina. The PFDN, is a national cooperative group of investigators at institutions across the country that perform research to find better ways to care for women with pelvic floor disorders, such as prolapse and urinary incontinence. The PFDN also includes a central Data Coordinating Center and Telephone Interviewing Center.

This study will enroll 180 women at 8 medical centers in the United States. Up to 45 women in the San Diego area will be asked to participate here at UCSD.

You are being asked to take part in this research study because you have decided to have vaginal surgery to repair prolapse of the uterus and vagina (uterovaginal prolapse).

Uterovaginal prolapse happens when the uterus and vaginal wall bulges into or through the opening of the vagina. Women with prolapse can often feel a bulge at the vaginal opening; we call this feeling having "bulge symptoms." This study is being done because we do not know which of these two surgeries are better for treating uterovaginal prolapse. Randomized trials of these 2 surgeries performed with long-term follow-up, are needed to evaluate the safety and effectiveness of these two procedures.

This consent form contains the information you need to help you decide whether or not to be in this research study. The study visit, procedures, risks, inconveniences, discomforts, and other important information are described below. Please read this consent carefully and ask any questions you may have.

STUDY PROCEDURES

Baseline Study Visit:
You will be asked to sign this consent form. Your medical record will be reviewed and you will be asked about yourself and your medical history. Your height and weight will be recorded. A pelvic examination will be done to measure your prolapse. During the pelvic exam, you will be asked to bear down and measurements will be taken. This examination is typically done when you see a doctor for prolapse.

If the information listed above has already been done as a part of your clinical care we may collect that information from your medical record instead of repeating your examination.

Also at this visit we will ask you to complete some questionnaires about your symptoms and your quality of life. Depending upon the questionnaire, the study coordinator will ask you the questions or have you complete and return the questionnaire. Some of the questionnaires include personal and sensitive information such as questions about urination, your sexual function, and how you feel about your body or your daily life. You can refuse to answer any questions that you do not want to answer.

At the early visit before surgery, the study questions and questionnaires could add about 60 minutes of extra time to your regular visit.

Randomization
If you agree to participate in the study, you will be randomly assigned to one of two surgeries. You have an equal chance (50%) of being assigned to either one of the vaginal surgeries:

- Vaginal Hysterectomy and USLS (Uterosacral ligament suspension)

Or

- Hysteropexy (done with UPHOLD® LITE)

The Vaginal Hysterectomy involves removal of the uterus through the vagina. The Uterosacral ligament suspension procedure ties the remaining vaginal tissue to supportive ligaments in the pelvis.

The Hysteropexy with UPHOLD® LITE procedure uses the UPHOLD® LITE mesh kit to support the uterus and upper vagina. The mesh is attached to the cervix.

The surgical assignment (randomization) will occur in the operating room on the day of your surgery. Neither you nor your doctor will choose whether you will have the vaginal hysterectomy and USLS or hysteropexy (done with UPHOLD® LITE).

You will not know which surgery you had during the course of the study, but at the end of the study, in approximately 5 years, when the results are made public, you will be told which surgery you had. If for any medical reason you need to know which surgery you received before the end of the study, we will tell you at that time.
If you have any bleeding or gynecologic concerns during the study, please contact the study physician or study staff and we will perform an evaluation.

You will also be given a 'SUPeR' Participant Wallet Card" that can be given to any medical provider who needs to contact us regarding your uterine status.

Follow-Up Study Visits:
We will collect study data in the hospital and all study participants will be seen up to 11 times after surgery. When possible, these visits will be timed to coordinate with your routine visits to see your surgeon.

The follow-up visits will be at the following times after surgery:

- 6 weeks
- 6 months
- 12 months
- 18 months
- 24 months
- 30 months
- 36 months
- 42 months
- 48 months
- 54 months
- 60 months (i.e. 5-years)

At every 6 month follow-up visit, a pelvic exam that measures your pelvic support will be done by an experienced examiner who is not your study surgeon. Also, during the visit, the study coordinator will ask how you are doing in general, about any gynecological or urinary problems, and about any medical care you have received since the previous visit. You will also be asked to complete questionnaires about your symptoms and quality of life. Each of these visits is expected to take about 45 minutes.

In order to find out whether there are different costs to the treatments in the long-term, the research staff will collect medical billing codes for the medical care you will receive at this hospital/clinic UCSD during the period of this study.

How long will I be asked to participate in the study?
Depending on when you enrolled in the study, your participation may last for up to 60 months (5 years) from the time of your prolapse surgery.

Will I receive any other information about my participation in the study?
If the researchers learn of significant new findings during the study that may affect your willingness to continue to participate, they will contact you.

POTENTIAL RISKS AND BENEFITS OF THE STUDY

What risks are there in participating in the study? What will be done to watch for or cut down on these risks?
Your surgeon will talk to you about the risks involved with your prolapse surgery. Both surgical procedures in this study are accepted standard surgical care for uterovaginal

prolapse and the surgeries themselves are not experimental. Both surgical procedures have the common surgical risks of infection, bleeding, damage to adjacent organs, and anesthetic complications. Both of the surgeries haves the anticipated benefit of providing relief of the prolapse symptoms of bulge, pressure, and vaginal discomfort. Most patients have improved sexual function after prolapse surgery and both of these procedures would be expected to provide that benefit.

Your surgeon is experienced in doing both of the surgeries (hysterectomy with USLS and hysteropexy with UPHOLD® LITE) we are studying. Both surgeries are performed through the vagina and do not require any abdominal incisions. It is anticipated that the time to complete the surgery (approximately 60- 90 minutes) is similar for each of the procedures and the length of hospitalization (usually overnight) and recovery from surgery is similar. Both procedures usually allow a return to routine daily living activities within a few days although complete recovery can take 4-8 weeks. Based on available information, we believe the overall risks and benefits for the two prolapse surgeries are similar, but each procedure has different specific risks and benefits.

Potential Risks and Benefits of the two procedures in this study

	Hysterectomy and USLS	**Hysteropexy with UPHOLD® LITE**

Potential Risks	• Intra-abdominal bleeding
	• Bowel injury
	• Bowel adhesions which could cause bowel obstruction
	• Slightly shorter vagina
	• Slightly higher risk of ureter injury (the tube that carries urine from the kidneys to the bladder)
	• May not be as durable because it involves only sutures and your own tissue
	• Earlier menopause (if premenopausal)
	• Need for additional surgery
		• Risk of future cervical or uterine abnormalities - bleeding, pre-cancer or cancer of the uterus or cervix, that may require future surgery
		• Mesh complications*
		  ○ Mesh erosion into the vagina or other organs
		  ○ mesh removal
		  ○ vaginal shortening
		  ○ vaginal tightening
		  ○ vaginal pain
		  ○ pain with sex including pain for male partner
		  ○ need for additional surgery

Potential Benefits	• Eliminate risk of future cervical or uterine abnormalities(bleeding, pre-cancer or cancer of the uterus or cervix) • No risk of mesh complications (erosion, vaginal shortening, vaginal tightening, vaginal pain, pain with sex)	• Preserves normal cervix, uterus, and upper vagina • Preserves current sexual response (e.g. uterine contractions during orgasm) • Decreased risk of intra-abdominal complication (bleeding , bowel injury, or bowel adhesions) • Possibly a more long lasting prolapse repair because of extra support from the mesh

*Potential mesh complications are a controversial topic and have been the topic of an FDA Safety Communication in 2011. The UPHOLD® LITE hysteropexy procedure that will be performed in this study involves the transvaginal placement of surgical mesh for pelvic organ prolapse but only a small amount of mesh is placed in a very limited way that we think minimizes the risk of mesh complications. Nevertheless, you may have seen TV advertisements from law firms recruiting patients for class action law suits against manufacturers of transvaginal mesh for prolapse. Usually, mesh is used with the goal of increasing the durability of a repair (i.e., decreasing the risk of prolapse happening again) Mesh is used when native tissue (suture repairs) may not provide long lasting results. There does appear to be an anatomic benefit when transvaginal mesh is used on the anterior vaginal wall (bladder side of the vagina).
We think it is important that you understand the risks/benefits of transvaginal mesh. The most common risks of transvaginal mesh are mesh erosion or exposure of mesh in the vagina, pain during sexual intercourse, and vaginal pain at times other than intercourse.

When the FDA reviewed the literature and reported on the safety of transvaginal mesh for pelvic organ prolapse in July, 2011 they reported:

- Patients who undergo prolapse repair with permanent mesh are subject to mesh-related complications that are not experienced by patients who undergo traditional surgery without mesh.
- Adverse events associated with transvaginally placed mesh can be life-altering for some women; sequelae (e.g., pain) may continue despite mesh removal.
- Mesh-associated complications are not rare. The most common mesh-related complication experienced by patients undergoing transvaginal prolapse repair with mesh is vaginal mesh erosion. Ten percent of women undergoing transvaginal prolapse repair with mesh experienced mesh erosion within 12 months of surgery.
- Women who experience erosion from synthetic mesh may require surgical excision in the operating room and it may require more than one procedure.
- Mesh contraction, causing vaginal shortening, tightening, and/or vaginal pain in association with transvaginal prolapse repair with mesh, is increasingly reported in the literature.
- Transvaginal surgery with mesh to correct vaginal apical prolapse is associated with a higher rate of complication requiring reoperation and reoperation for any reason compared to traditional vaginal surgery or abdominal mesh suspension of the vagina.

<u>It is important to note that the mesh warnings above were warnings against all mesh kits, many of which are no longer on the market.</u> We think the UPHOLD® LITE mesh system used in this study has a much lower risk of mesh related complications for the following reasons:

- The mesh used in this study minimizes the amount of mesh in the vagina; the UPHOLD® LITE device contains the smallest amount of mesh currently available in transvaginal mesh kits.
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- The mesh used in this procedure only uses mesh at the very top of the vagina to minimize the risk of pain with intercourse. No mesh is placed along the back wall of the vagina and very little mesh extends from the cervix towards the front wall of the vagina.
- The incision used for this surgery is placed such that the mesh is not next to the incision line and therefore the reported mesh erosion rates with this device (less than 2%) are much lower than overall 10% erosion rates reported with other devices
- The mesh is directly attached to the supporting ligaments. It does not use long needle (trocar) applications that put mesh closer to the bladder and rectum and increase the risk of bladder or rectal injury and put mesh in places it is not needed.
- There may be a benefit if the uterus is not removed for increasing the strength of the repair, and this can only be done with the addition of mesh. Also, it offers women the option of keeping their uterus if they want to.

For both procedures, we will minimize the chance of complications from injuring the ureter or the bladder by looking inside your bladder at the end of surgery (known as cystoscopy) to make sure that urine is flowing through the ureters from both kidneys into the bladder.

Questionnaires and interviews:
The quality of life interviews contain items that are of a personal nature and may make you uncomfortable. You may refuse to answer any question that you do not want to answer. There is also a risk of loss of confidentiality. The section below entitled 'Confidentiality of Study Records' describes procedures we have in place to minimize this risk.

What happens if you are injured as a result of the study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 657-5100 for more information about this, to inquire about your rights as a research subject or to report research-related problems.

If you participate in this study, can you also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without talking it over with the researchers involved in each study.

Are there benefits to taking part in the study?
If you agree to take part in this study, there may or may not be direct medical benefit to you. However, by participating in this study, we hope that the information obtained from this study will help us decided if one of these standard surgeries is better than the other. Ultimately, this will improve the medical care offered to women with prolapse like yours.

FINANCIAL INFORMATION

Who is funding the study?
This study was developed by the Pelvic Floor Disorders Network (PFDN), which is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); the National Institutes of Health Office of Research on Women's Health and Boston Scientific Corporation. This means that UCSD and the Data Coordinating Center receive payments from these agencies to support the activities needed to do this study. None of the researchers will receive a direct payment or increase in salary for conducting this study. The U.S. Food and Drug Administration (FDA) has reviewed this study and provided recommendations.

What is the involvement of Boston Scientific Corporation?
Boston Scientific Corporation is providing funding to the National Institutes of Health for some expenses related to performing the study and is selling the devices to the study sites at a discounted rate. Boston Scientific Corporation may or may not benefit from this study depending on the results of the study.

Will it cost you anything to participate in the study?
The surgery and physician visits at baseline, hospital discharge, and 6 weeks are part of standard clinical care and will be billed to your insurance in the usual manner. The study will pay professional fees related to some parts of the surgery and evaluation of tissue by a pathologist if tissue is removed. This may decrease costs to your insurance company or possibly you. There are no increased costs to you as a result of participation in this study. If your bladder or bowel symptoms get worse following surgery, or if other complications after surgery occur, all costs associated with the treatment of these complications are considered part of your standard clinical care and will be billed to you or your insurance company. Although your surgeon may typically want to see you for follow up after 6 weeks, the remaining visits beginning at 6 months after your surgery and continuing every 6 months will be considered study visits and paid for by the study.

Will I be paid or given anything for being in the study?
Depending on when you enroll in this study, you will be paid between $550 and $950, to offset the cost to you for travel, parking, and your time. Everyone in this study will be followed at least 36 months after surgery, and if you complete all the visits up to 36 months, the payment total would be $550. Early participants, those who enrolled in the first 6 months of the study, could be followed as long as 60 months and then the payment total will be $950. This will be provided as follows:

- $50 following completion of the baseline, 6-week, and 6, 12 and 18 month study visits ($50 x 5);
- $100 following completion of 24, 30, 36, 42, 48, 54 and 60 month study visits ($100 x 7).

Conflict of Interest
Your doctor may be an investigator in this research study and, as an investigator, is interested both in your medical care and in the conduct of this research. Before entering this study or at any time during the research, you may discuss your care with another doctor who is not associated with this research project. You are not under any obligation to participate in any research study offered by your doctor.

ALTERNATIVES TO PARTICIPATING IN THE STUDY

You do not have to participate in this study to get health care at this medical center. You may choose to have either surgical procedure without participating in the study. Ask your study doctor to talk about the options with you along with their risks and benefits.

ENDING THE STUDY

If you want to withdraw from the study, what should you do?
You do not have to take part in this research study and, should you change your mind, you can withdraw from the study at any time. If you decide to leave the study early, please contact Dr. Lukacz or the study coordinator in person or at (858) 657-6827 to tell us that you would like to withdraw (end your participation in the study). While you are not obligated to, we would appreciate it if you would do the end-of-study telephone interview when you withdraw.

If you decide to leave the study early, what is likely to happen to you? Are there likely to be any dangers in doing so?
You may end your participation and withdraw your consent at any time. Your decision will not in any way affect the medical care available to you now or in the future or results in loss of benefits to which you are entitled. We may ask you to complete a final quality-of-life interview. If you have any problems related to your participation in this study you will be followed by your physician and offered management options if necessary.

What are some of the reasons why the researchers might take you out of the study even if you want to continue to participate?
Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. Your study doctor may choose to take you out of the study because of unexpected or serious side effects or if you are unable to follow study instructions.

Study participants will be informed of all relevant new findings.

CONFIDENTIALITY OF SUBJECT RECORDS

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access.

How will the researchers protect your privacy?
Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed

outside of UCSD. Records disclosed outside of UCSD will be 'de-identified' which means they will be assigned a unique study ID number. The key to the study ID number assignment and information you have provided will be kept in a research record and stored in a locked cabinet and on a secure, password-protected computer. Research information will not be made a part of your regular medical record.

What information will be disclosed?
As part of this study, Dr. Lukacz and her study team will ask you to have certain tests. Some of this testing would have been done as part of your regular care. He will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the PFDN DCC. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record.

If you have an emergency room visit or hospitalization at a facility outside of the UCSD system we will ask you to sign a medical records release and this information will be requested from that institution. This information will also be de-identified when disclosed outside of UCSD.

As part of the study your name and contact information will be disclosed to the QOL center, via a secured and encrypted website, so they may contact you for your study related telephone interviews. No clinical study information will be disclosed to the QOL center, only your contact information.

Billing information and discharge summaries for clinical care visits (including emergency room visits and hospital admissions) related to your prolapse procedure will be collected, de-identified and reported to the DCC.

Who else might see information about me collected during the study?
The following people may see research information collected during the study:

- the researchers may need information to make sure you can take part in the study, to check your test results, or to look for side effects related to the research;
- institutional or government officials may need to see information to make sure the study is done properly; this may include individuals from the FDA and the study sponsors (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the Office of Research on Women's Health
- Boston Scientific Corporation may use results collected from this research to submit to the FDA upon request;
- clinical monitors from the Data Coordinating Center may review your research and medical files to make sure that the study is done properly;
- safety committees of the Pelvic Floor Disorders Network may review research information to make sure the study is conducted safely and properly; and
- because you will receive money for participating, the institution's accounting department may need to see information for tax reporting purposes.

A description of this clinical trial (Identifier # NCT 01802281) will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What happens to information about me after the study is over or if I cancel my permission?

As a rule, researchers will not continue to use or disclose information about you but will keep it secure until it is destroyed. However, even after the study is complete or after you decide to withdraw from the study, information about you may be used or disclosed as follows:

- To avoid losing study results that have already included information collected about you during the study;
- To provide information, that does not include your name, social security number, or other identifying information for research, educational or other lawful activities;
- To help institutional and government officials make sure the study was conducted properly;
- As required by applicable federal or state law. For example, if you withdraw from the study at any time, a record of your withdrawal and the reasons you gave for withdrawing will be kept as part of the study record.

What happens to information about you after the study is over or if you cancel your permission?

Once your research records have been disclosed as described above, they may no longer be protected directly by federal privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"). However, as long as the information is held in any part of the Institution's system, it is protected by the Institution's privacy policies. For more information about these policies, please ask your doctor for a copy of the specific institution's Privacy Practices.

CONTACT INFORMATION

For more information about the study or the study procedures or treatments, or to withdraw from the study, contact: JoAnn Columbo at (858) 657-6827.

For Emergencies, your doctor (or a physician colleague covering for him/her) can be reached by calling the UCSD page operator at (619) 543-6737, 24 hours a day, 7 days a week.

For more information about your rights as a research subject, or to express a concern about the study, contact the UCSD Human Research Protection Program at: (858) 657-5100.

CONTACT FOR FUTURE RESEARCH SIGNATURES

There may be studies in the future that may be of interest to you. May we have your permission to contact you in the future to discuss other research projects? The person contacting you would be your physician or a member of UCSD's research team. Please initial below to indicate your permission regarding contact for future research.

_____ Yes, you may contact me in the future regarding research projects

_____ No, you may not contact me in the future regarding research projects

RECORD OF INFORMATION PROVIDED

A copy of the signed consent will be given to you. The original signed informed consent document will be kept with the research file. You will receive a copy of this document and a copy of "The Experimental Subject's Bill of Rights" to keep at the time you sign it.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to you. You have been allowed to ask questions, and your questions have been answered to your satisfaction. You have been told whom to contact if you have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. You have read this consent form and agree to be in this study, with the understanding that you may withdraw at any time. You have been told that you will be given a signed and dated copy of this consent form."

_____ _____

Signature of Participant **Date**

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent **Date**