MAGEE-WOMENS RESEARCH INSTITUTE & FOUNDATION

THE MAGEE-WOMENS RESEARCH INSTITUTE CLINICAL TRAINEE RESEARCH AWARD

FACE PAGE (must be typewritten)

APPLICANT INFORMATION	
NAME (Last, first, middle) [redacted]	DEGREE(S): MD ARE YOU A RESIDENT OR FELLOW: [redacted]
POSITION TITLE: [redacted]	OFFICE MAILING ADDRESS (building, room, street, city, state, zip code) [redacted]
YEAR(S) IN TRAINING: [redacted] YEAR(S) IN CURRENT PROGRAM: [redacted]	
DEPARTMENT [redacted]	
TEL: [redacted]	E-MAIL ADDRESS: [redacted]

APPLICATION TITLE:	Impact of L3SP on normalization of enlarged genital hiatus after minimally invasive sacrocolpopexy: a randomized controlled trial

HUMAN SUBJECTS RESEARCH ☐ No ☒ Yes	IRB APPROVAL DATE: pending
VERTEBRATE ANIMALS ☒ No ☐ Yes	IACUC APPROVAL DATE:
TOTAL FUNDS REQUESTED	$3000

FACULTY SPONSOR	DEPARTMENT CHAIR OR DIRECTOR OF FELLOWSHIP/RESIDENCY PROGRAM
Name [redacted]	Name [redacted]
Title [redacted]	Title [redacted]
SIGNATURE [redacted]	SIGNATURE [redacted]

APPLICANT SIGNATURE	DATE
[redacted]	1/10/19

PROPOSED BUDGET

Personnel – List **effort** for **all** personnel to be involved in carrying out the proposed research, whether or not salary is requested, **beginning with P.I.**

Name	Role	% Effort	Salary Requested	Fringe Benefits*	Total
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	$	$

Equipment	n/a	Subtotal	$0
Supplies (list)	Production Supplies (recruitment brochures)	Subtotal	$50.92
Other Expenses	Transperineal ultrasound (2 per subject x 6 subjects, $96.59/each)	Subtotal	$1159.08
		Total	$ 3000

*MWRIF Staff fringe benefit rate is 25.0%

BUDGET JUSTIFICATION

[redacted] is one of the research coordinators for the division of Female Pelvic Medicine and Reconstructive Surgery. She will help with study recruitment and enrollment. Additionally, she will assist in ensuring all preoperative and postoperative questionnaires are completed and will help monitor patient follow-up for the study period. She has assisted in multiple research projects through the division of Female Pelvic Medicine and Reconstructive Surgery, including other randomized controlled trials. We estimate that she will spend 1 hours of work on this project per week, which is equal to 2.5% of her total time (in hours) and thus, how we calculated the above budget.

We will use brochures about this study included in the patient pre-surgical packet of information. This will enable us to discuss the study and give the patient additional information about the study and time to think about the study to reduce coercion for recruitment.

We will perform transperineal ultrasound as an exploratory aim of this study. This is an important pilot component of this study; the information gleaned from this technology will augment the clinical outcomes otherwise evaluated in the study. Please see attached letter, page 8, for ultrasound budget agreement.

Abstract:
Objective: Evaluate whether patients undergoing a level III support procedure (L3SP) to reduce genital hiatus (gh) at time of minimally invasive sacrocolpopexy (MISC) will affect the proportion of women with enlarged postoperative gh at six months. An exploratory objective is to evaluate changes in the pelvic floor with or without L3SP with transperineal ultrasound (TPUS).
Design: Randomized controlled trial
Sample Size: 30 subjects per arm to detect a 25% difference between groups. Planned recruitment is 75 subjects to maintain >80% power with attrition.
Methods: Randomization in the operating room. Performance of L3SP in those randomized to concomitant surgery. Three subjects from each arm will have pre- and postoperative TPUS.
Results: Primary outcome is the proportion of subjects with an enlarged postoperative gh (>4cm) at 6 months. Secondary outcomes include recurrent prolapse, postoperative dyspareunia and sexual function. Pre- and postoperative TPUS levator hiatal area and pelvic floor shape will be compared.

Training Goals:

This proposed project by Dr. [redacted] will allow her to take an important first step in her research career and towards her long-term career goal of becoming an independent clinician-scientist. She has had prior research experience in retrospective studies as well as secondary analysis of prospectively collected data. As an applicant for the ICRE Master of Science in Clinical Research with emphasis on comparative effectiveness, she is proposing a prospective randomized clinical trial. This very important trial will help further our understanding of the necessity for a concomitant L3SP at the time of minimally invasive sacrocolpopexy. There is currently no standard to guide clinicians towards who will benefit from this procedure.

During this proposed project, Dr. [redacted] will learn invaluable skills regarding study design and clinical trial implementation. Since the project's inception, she has worked to develop a pragmatic trial with equipoise between the study groups. She has developed an important clinical question with a hypothesis-driven plan for answering this question. As PI, she will learn the importance of anticipating and preparing for potential issues during the implementation of the study. She will work with the attending physicians in the FPMRS group, co-fellows, research coordinators and statisticians over the course of the study. These are necessary skills to a future career as a surgeon-scientist.

In addition, she will gain experience with data analysis and manuscript preparation. In the proposal she has already gained skills with power and sample size calculations as well as randomization schemes and the process of masking and blinding. During this project she will gain a better understanding of what statistical tests to run and which software is needed to run them. All of this will culminate in a planned national conference presentation of her research findings as well as preparation of a manuscript for submission to a peer-reviewed journal.

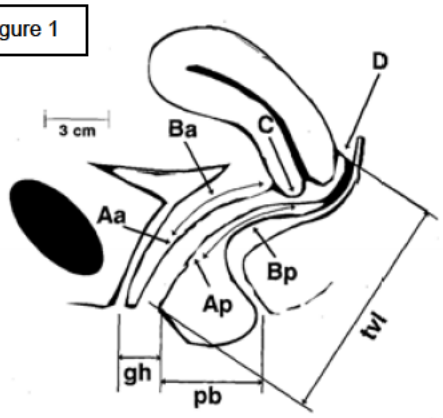
This project will be an important aspect of Dr. [redacted] oral sub-specialty boards for Female Pelvic Medicine and Reconstructive Surgery as she will need to defend this research study design, implementation and results. This project will highlight the importance of relevant research in our field and hopefully encourage Dr. [redacted] to develop additional project proposals.

Dr. [redacted] will be the primary investigator with significant support from an experienced research team including Dr. [redacted] and myself. Dr. [redacted] is a prominent researcher in the field of sacrocolpopexy biomaterials and pelvic floor imaging. As Dr. [redacted] primary mentor I am committed to meeting on a regular basis throughout the award period to ensure adherence to her timeline, budget and troubleshoot issues like subject recruitment and retention.

A. Significance:

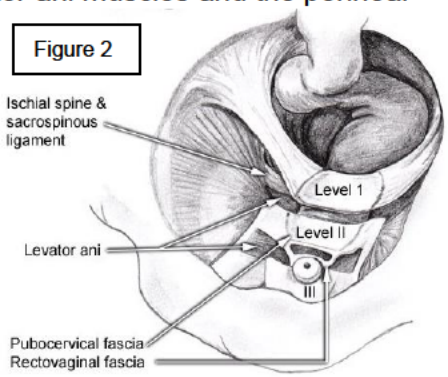
In the United States, it is estimated that 12.6% of women will undergo surgery for pelvic organ prolapse (POP) by age 80 and the incidence of reoperation for recurrent prolapse increases with age.[1,2] When evaluating pelvic organ prolapse, the most accepted format of quantifying the amount of prolapse is via the Pelvic Organ Prolapse Quantification system (POP-Q).[3] The nine points of measure are noted in Figure 1: the genital hiatus (gh) and perineal body (pb) can be seen here, as well as the measures for the anterior vaginal wall, Aa and Ba, and the posterior vaginal wall, Ap and Bp.[3] Gh is measured from the middle of the external urethral meatus to the midline posterior vaginal hymen. Pb is formed from a combination of the superficial perineal muscles, the levator ani and the anal sphincter complex. It is thought that an enlarged gh and a short pb predispose women to POP.[4]

Figure 1



We know that the apex of the vagina is supported by the cardinal-uterosacral ligament complex (level I support), the mid-vagina is supported by lateral attachments to the arcus tendinous and the fascia of the levator ani muscles (level II support). The lower third of the vagina is supported by the perineal membrane, levator ani muscles and the perineal muscles (level III support) (Figure 2).[5] POP surgical treatments are aimed at repairing these defects in the support of the vagina via a variety of non-mesh (native tissue) or mesh based procedures.[6] Sacrocolpopexy, in its modern form, is a minimally invasive, mesh-augmented prolapse reconstruction that repairs support for levels I and II of the vagina. Although minimally invasive sacrocolpopexy (MISC) is a durable prolapse repair,[7] recurrent prolapse can still occur. Rates vary in the literature from 6.4% to 23.2%[8–10] with the majority of recurrences after MISC in the posterior vaginal compartment, thought to be level II and III defects.[10,11]

Figure 2



If a patient were to experience symptomatic posterior compartment prolapse after MISC, they may undergo a level III support procedure (L3SP) known as a posterior colporrhaphy and/or perineorrhaphy aimed at repairing the distal vaginal support. These procedures repair the fibromuscularis tissue supporting the posterior vaginal wall, the muscles of the levator ani, and perineal body to reduce the posterior compartment prolapse and relieve obstructed defecation symptoms. In addition to general operative risks, de novo dyspareunia may be a risk after a L3SP.[12–14]

Currently, some surgeons may choose to perform a L3SP at the time of MISC to decrease the risk of symptomatic recurrent POP, but this approach is surgeon- and medical center-specific with significant variability in the literature without prospective, standardized trials.[15–17] Several retrospective studies and secondary analyses of prospectively collected data have shown that an enlarged preoperative gh is associated with an increased likelihood of prolapse recurrence after native tissue repair and MISC.[8,18–20] If the gh is enlarged, it is generally thought to indicate underlying levator muscle damage.[21] When surgeons perform L3SP, they attempt to repair defects in the levator ani complex as well as add bulk and substance to the perineal muscles. Conceivably, if the gh is thought of as a hernia portal for POP, then decreasing the size of the portal via a level III support procedure should decrease the risk of recurrent POP.

The argument against a concomitant L3SP is that the apical suspension procedure, like MISC, may serve to reduce the gh size without a concomitant L3SP.[20] Studies in patients undergoing native tissue repair have shown that a posterior colporrhaphy, which may impact gh size, did not decrease chance of recurrent prolapse.[18] There is significant variation in what a surgeon may describe as a L3SP and we do not currently understand what muscles are brought together by a L3SP or what portion of the levator muscles may be altered by the apical suspension alone. Transperineal ultrasound can be used to evaluate the levator muscles, but this modality has not been explored for postoperative patients. If we can improve our understanding of which patients may benefit from a L3SP procedure at

the time of MISC and what changes are occurring on a muscular level, this would allow for a more standardized approach to this clinical question.

B. Specific Aims

a. **Aim 1.** Evaluate whether concomitant L3SP at time of minimally invasive sacrocolpopexy is necessary to significantly affect the proportion of women with enlarged 6-month postoperative genial hiatus (>4cm).
   i. Hypothesis: Women with an enlarged preoperative gh (≥4cm) who undergo concomitant L3SP with MISC will have a significantly decreased risk of enlarged gh at 6 months postoperatively as compared to women who do not have a L3SP.

b. **Aim 2.** Evaluate overall postoperative sexual function and specifically dyspareunia after sacrocolpopexy with and without concomitant L3SP.
   i. Hypothesis: Women with an enlarged gh (≥4cm) who undergo concomitant L3SP with MISC will have similar overall postoperative sexual function and dyspareunia rates as compared with women who do not undergo this procedure.

c. **Aim 3.** Evaluate the preoperative and postoperative levator hiatal area for subjects with and without concomitant L3SP and sacrocolpopexy on transperineal ultrasound.
   i. Hypothesis: Women with sacrocolpopexy and concomitant L3SP will have a significantly smaller levator hiatal area as compared with women treated with sacrocolpopexy alone.

C. Experimental Design - This is a randomized, controlled trial evaluating women undergoing minimally invasive sacrocolpopexy for pelvic organ prolapse with a preoperative enlarged genital hiatus (defined as greater than or equal to 4cm). Participants will be randomized if intraoperative gh obtained at the completion of mesh tensioning for MISC is enlarged (between 4.0 and 7.5cm). A planned pilot study to invite six enrolled subjects (ideally three from each arm of the study) to undergo both a preoperative (less than 3 months prior to surgery) and a 6-month postoperative transperineal ultrasound examination.

Statistical Considerations and Analytic Plan: The proportion of subjects with persistently enlarged gh will be compared between the randomized groups using chi-square and a multiple variable logistic regression model including independent variables for our dichotomized gh groups (gh <4cm, gh ≥ 4cm). The composite outcome will be created using objective measures of recurrence (any POP-Q measure ≥0 at any postoperative visit), subjective measures of recurrence ("Do you usually have a bulge…" on Pelvic Floor Distress Inventory-20) and any retreatment with pessary or surgery for symptomatic prolapse to 24 months postoperatively. Sexual Function will be assessed using the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, IUGA Revised questionnaire and will be compared between surgical treatment groups using repeated measures analysis of covariance. Dyspareunia outcomes will be tabulated in the affirmative or negative and we will evaluate for differences between baseline and postoperative using tests of symmetry.

Transperineal ultrasound will be performed on subjects from both randomized surgical groups. Images will be acquired in the mid-sagittal plane at rest and maximum Valsalva effort to measure levator hiatal area. Mean area will be compared before and after surgery to determine whether support of the apex via sacrocolpopexy decreases the size of the levator hiatus and +/- L3SP to compare the size of the hiatus between the two surgical treatment groups using paired samples t-test.

Power analysis: Based on UPMC FPMRS Division data from 2009 to 2019, we can assume that 1% of women with a L3SP will have an enlarged postoperative gh. To achieve 80% power, we will need 30 subjects per arm to detect a 25% difference in proportion of patients per group with an enlarged postoperative gh. With an assumption of 20% attrition rate, we plan to recruit 75 subjects to maintain sufficient power.

Timeline: This project requires recruitment of 75 subjects based on our projected power analysis and assumed attrition rate of 20%. We performed 149 sacrocolpopexies in the division of Urogynecology in the last 12 months, with historic data showing 79% (n=119) of our patients meet inclusion criteria. We aim to complete enrollment in this study within 1 year based on this data and will have primary outcome analysis completed by 7 months following the last patient's surgery. I am currently a first year fellow and should have sufficient time in my three year fellowship to complete this project if I start recruitment as planned in early 2020.

References (not to exceed 25 references)

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January 10, 2020

[redacted]

Dear Dr. [redacted]

This brief note serves as a letter of support and commitment for your grant application entitled “Impact of L3SP on normalization of enlarged genital hiatus after minimally invasive sacrocolpopexy: a randomized controlled trial”. As previously discussed, I will participate in the technical aspects of applying the use of ultrasound technology as well as interpreting the data and will be providing this service for $97/patient. I look forward to assisting you in this project.

Sincerely,

Noedahn Copley-Woods, MD
Division of Ultrasound
Magee-Womens Hospital
University of Pittsburgh