Long-Term Effectiveness Of Sacrospinous Ligament Fixation (SSLF) versus Uterosacral Ligament Suspension (ULS) With and Without Perioperative Behavioral Therapy/Pelvic Muscle Training: The Extended Operations And Pelvic Muscle Training In The Management Of Apical Support Loss

E-OPTIMAL

PFDN Protocol 16P01S
Amendment 2: 02/23/2015

Approvals:

Concept: 4/23/09
Mini-Protocol: 5/22/09
Steering Committee: 7/23/09
Advisory Board: NA
DSMB: 9/16/09
Final: 2/11/10
Amendment 1: 5/5/2011

Protocol Committee:

Cleveland Clinic: J. Eric Jelovsek and Matthew D. Barber (Co-Chairs)
Loyola University: Kim Kenton
Duke University Medical Center: Alison Weidner
University of Alabama at Birmingham: Holly Richter,
University of California-San Diego: Shawn Menefee
University of Texas Southwestern: Joe Schaffer
University of Utah: Ingrid Nygaard,
University of Michigan: Cathie Spino, Nancy Janz
NICHD: Susan Meikle

TABLE OF CONTENTS

PROTOCOL AMENDMENT 1
Effective Date: May 5, 2011
The following list includes the changes in Amendment 1:

1) **Revise Title page**
   Delete: ~~DCC~~ from **University of Michigan:** Cathie Spino, Nancy Janz
   Insert: No insertion
   Rationale: University of Michigan is no longer the DCC.

2) **Table of Contents**
   Insert Amendment 1

PROTOCOL AMENDMENT 2
Effective Date: February 23, 2015
The following list includes the changes in Amendment 2:

1. Section H.1.i the following was added: If patients have not completed the yearly QOL phone interview the site will administer the POPDI subscale of the PFDI as this is necessary for the primary outcomes D1.1 and D2.1)
2. Timeline of visits table was updated to reflect item 1.

A. STUDY AIMS

The goal of this long-term follow-up study is to extend the follow-up of women in the OPTIMAL study up to 5 years from the time of surgery and to compare the success and complication rates of the two surgical treatment groups over this extended time period. The Operations and Pelvic Muscle Training in the Management of Apical Support Loss (OPTIMAL) study is a randomized trial designed to compare sacrospinous ligament fixation (SSLF) to uterosacral vaginal vault ligament suspension (ULS) and to assess the role of perioperative behavioral therapy/pelvic muscle training (PMT) in women undergoing vaginal surgery for apical or uterine prolapse and stress urinary incontinence (SUI).[1] The OPTIMAL study includes a two-year follow up from the time of surgery, which is too short to evaluate the long-term sequelae of the surgical procedures. A further goal of E-OPTIMAL is to investigate a strategy for improving enrollment and retention in long-term studies of women undergoing surgery for pelvic organ prolapse and SUI, by randomizing subjects to two different recruitment methods.

The primary aims of this extension study are to compare SSLF and ULS for the following outcomes up to 5 years after surgery in women with Stage 2-4 prolapse involving the vaginal apex or uterus and stress urinary incontinence:

1. time to surgical failure;
2. the long-term functional and health-related quality of life (QOL), adjusted for PMT treatment group;
3. the annual and cumulative incidence, resolution, and persistence of pelvic floor symptoms (urinary, bowel, and prolapse), adjusted for PMT treatment group.

An additional primary aim (aim 4) is to determine whether exposure to a standardized video detailing the importance of long-term follow-up studies for pelvic organ prolapse prior to the informed consent process will improve enrollment and/or retention in E-OPTIMAL. We will utilize a conceptual framework that assesses three concepts (motivation, barriers and pragmatic issues) at two levels (study level and personal/individual level). This conceptual framework was developed following a review of the scant available literature on the topic, as well as during discussions with investigators who are experienced in recruiting and retaining participants in pelvic floor disorders studies.

The secondary aims of this study are:

1. To describe the recurrence, reoperation, and re-treatment rates for any pelvic floor dysfunction and for prolapse only, and identify their predictors by surgical intervention and PMT intervention.
2. To determine independent risk factors (e.g., age, co-morbidities), in addition to anatomic surgical failure at 2 years, for new or worsening pelvic floor symptoms (based on the MID of UDI and 0.5 effect size of POPDI and CRADI) over time (years 3-5 after surgery).
3. To describe the annual and cumulative incidence, resolution, and persistence of pelvic floor support in each compartment (anterior, posterior, and apex) by surgical intervention and PMT intervention.
4. To describe the rate of long-term negative outcomes related to SSLF and ULS, including suture and mesh erosion.
5. To describe the long-term effect of PMT on pelvic muscle strength and determine its correlation with symptom resolution

6. To describe the motivation and barriers for individual women's participation in women's health research as well the specific E-OPTIMAL study.

We propose to test the following null hypotheses:

1. There will be no difference in time to surgical failure between ULS and SSLF up to 5 years after surgery (Specific aim 1)
2. The addition of a standardized video detailing the importance of long-term follow-up studies for POP to the informed consent process will not improve enrollment or retention in E-OPTIMAL (Specific aim 4).

The other primary aims of the study will be addressed through estimation approaches, and testing approaches that are not adjusted to control for the study-wide Type I error.

B. BACKGROUND AND SIGNIFICANCE

Long-term outcomes of vaginal prolapse surgery

Few studies assess postoperative outcomes more than two years after vaginal prolapse surgery. The rare studies that do are limited by retrospective and non-comparative study designs, small sample sizes, inconsistent nomenclature, inconsistent and non-standardized pelvic examinations, non-standardized follow-up, and lack of information on coexisting pelvic floor disorders. A recent systematic review on apical vaginal prolapse surgery reported a mean follow up of 32.6 $\pm$ 19.8 months.[2] Forty-two studies were identified that evaluated ULS or SLS and many of these studies are listed in Tables 1 and 2. The only prospective study with follow-up beyond 2 years was the clinical trial by Benson et al. (mean follow up of 2.5 years).[3] Andre Silva et al. retrospectively evaluated postoperative anatomic and functional outcomes of the high uterosacral ligament vaginal vault suspension between 3.5-7.5 years.[4] Surgical failure, defined as symptomatic recurrent prolapse of POP-Q Stage 2 or greater in one or more segments, was 11/72 (15.3%). Female Sexual Function Index scores for arousal, lubrication, orgasm, satisfaction, and pain were normal and desire was abnormal. A second study performed by Paraiso et al. evaluated 243 patients who underwent sacrospinous ligament suspension from 1978-1991 at a single institution. Mean length of follow up was 73.6 months.[5] Approximately 102 (42%) failed in at least one vaginal segment and apical defects were seen in only 20 (8.2%). Reoperation rates were 4.5%. Although this study reported time to failure of prolapse surgery 1, 5, and 10 years (88%, 79%, and 52%), it was retrospective in design. It is also unclear in the current literature whether delayed, post-operative pelvic floor dysfunction symptoms reflect surgical failure, the inexorable progression of neurologic or structural weakness inherent in women with POP, or the contribution from medical or social comorbidities that increases with age.

Women enrolled in OPTIMAL provide a unique population to compare the longer-term effectiveness of two surgical procedures performed using the vaginal approach for pelvic organ prolapse, as well as to study the natural history of women who have undergone surgery for advanced prolapse using two different vaginal approaches. E-OPTIMAL will address many of the limitations of the existing literature. This extended prospective follow-up of the OPTIMAL trial will include a large sample of women of various ethnic and socioeconomic backgrounds who have undergone two standardized approaches to performing SSLF and ULS, making the findings generalizable to the population of women with POP who undergo vaginal surgery. Standardized, validated assessment tools will be used to determine objective and subjective findings. Personnel who are not involved in the patient's medical care will perform assessments.

Additionally, this long-term study provides a unique opportunity to evaluate different methods of improving long-term retention in studies of women undergoing vaginal reconstructive surgery.

Despite the well-recognized need for long-term follow-up studies in pelvic reconstructive surgery, there is little understanding of individual's motivation and barriers to participating in long-term surgical studies. One potential strategy to improve clinical trial recruitment and retention is the use of an audio-visual presentation of information about the disease under study and the details of the trial to augment the informed consent process. This approach recognizes that potential participants may be overwhelmed with the amount of information they receive; in addition, certain individuals absorb information preferentially by a visual communication ("visual learners"). The use of video-assisted recruitment strategies are poorly understood and have been identified in a recent Cochrane review that identified 4 randomized or quasi-randomized trials evaluating this strategy. [6] While the results were mixed, one study found that audio-visual presentations enhanced the quality of information conveyed to study participants[7] and another demonstrated better retention of knowledge about the intervention compared to standard informed consent.[8] Moreover, in one multi-center trial, the Term Prelabor Rupture of Membranes (Term PROM) study, more women who watched an instructional video prior to the informed consent process were willing to participate in the study than those who underwent the standard informed consent process alone (62% vs. 35%). [8] In contrast, some studies demonstrated no benefit to video or multi-media intervention on knowledge. The Cochrane reviewers encouraged investigators to continue to explore innovative methods of providing information to potential trial participants and emphasized the need for high-quality randomized trials with clear reporting of methods.[6] E-OPTIMAL presents a unique opportunity to evaluate the use of a standardized video detailing the importance of long-term follow-up studies for POP to augment the informed consent process to determine if it will improve enrollment and retention in this long-term study of prolapse surgery.

C. STUDY OVERVIEW

Women will be invited to participate in E-OPTIMAL at their last clinical follow-up visit for OPTIMAL (at 24 months post surgery). E-OPTIMAL is an extension of the ongoing OPTIMAL study and no new study treatment interventions will be given. Rather an enrollment intervention will be investigated with potential E-OPTIMAL participants randomly assigned to watch a standardized video prior to consent or undergo the standard informed consent process for primary aim 4. The standardized video will review the rationale for women's health research, the importance of long-term follow-up and a detailed invitation to participate in E-OPTIMAL. The video has undergone review by potential subjects, coordinators and physician researchers to ensure that the relevance and importance of issues potentially impacting on long-term participation in studies such as E-OPTIMAL are covered. Participation in E-OPTIMAL will occur up to three additional years. Women will be strongly encouraged to participate in annual examinations and annual telephone surveys but may participate in only one of these study parts if needed.

D. OUTCOME MEASURES

The measures described below (with the exceptions noted) are instruments that are used by OPTIMAL and will enable us to analyze the data longitudinally over time.[1]

D1. Surgical intervention

D1.1 Primary outcome measure

The primary outcome measure for the surgical intervention of OPTIMAL is surgical "success" or "failure" as a dichotomous outcome at 2 years (defined below). For E-OPTIMAL, the primary outcome measure is the time to surgical failure using the definition of surgical failure as used in OPTIMAL.

The definition of surgical failure has 2 components:

1. anatomic assessment of prolapse, using the Pelvic Organ Prolapse Quantification (POPQ) system[9] and
2. the presence or absence of bulge symptoms specific to prolapse, using two questions from the Pelvic Floor Distress Inventory (PFDI)[10].

For OPTIMAL study eligibility, all subjects must report bothersome bulge symptoms at baseline; therefore, the symptom component of the primary outcome measure is based on the persistence (postoperative presence) or resolution (postoperative absence) of the baseline bothersome bulge symptoms. A subject will be considered a surgical failure if any ONE of the following criteria is met:

a. If POPQ point C descends more than one-third of TVL (C > -2/3*TVL; i.e., when TVL=9, -5 is a failure by this criterion but -6 is not a failure), or
b. if POPQ points Aa, Ba, Ap or Bp are > 0 cm, or
c. if the subject reports bothersome vaginal bulge symptoms (see definition below), or
d. if the subject undergoes surgery for prolapse or elects to use a pessary for prolapse at any point during the follow-up period.

Otherwise, a subject will be considered a surgical "success."

Subjects will be considered as having bothersome vaginal bulge symptoms if they report a positive response to either questions 4 or 5 of the PFDI AND any degree of bother (i.e., any response other than "not at all" to the question "How much does this bother you?"):

a. Question 4: Do you usually have a sensation of bulging or protrusion from the vaginal area?
b. Question 5: Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?

D1.2 Secondary outcome measures

Efficacy

1) Anatomic outcomes of each vaginal segment (anterior, posterior, and apical) assessed by their corresponding POPQ point (Ba, Bp, C) measured as continuous variables.
2) Time to anatomic prolapse recurrence (time to failure)
3) Time to symptomatic prolapse recurrence (i.e. vaginal bulge symptoms) (time to failure)
4) Pelvic symptoms:
    a. Urinary function: change from baseline in UDI scores[10] to assess general urinary function and Hunskaar Incontinence Severity Index[11] to specifically assess the presence and severity of urinary incontinence . Additionally, subjects will complete the Patients Global Impression of Improvement (PGI-I)[12] to assess global improvement of bladder function.
    b. Bowel function: change from baseline in CRADI scores [10]
    c. Prolapse symptoms: change from baseline in POPDI scores [10]
5) Re-operation rates

a. Re-operation for complications
b. Re-operation for prolapse
c. Re-operation for stress urinary incontinence (includes periurethral bulking injections)

6) Non-surgical treatment for pelvic floor disorders
   a. Pessary use for prolapse
   b. Stress urinary incontinence
   c. Urge urinary incontinence and other overactive bladder symptoms
   d. Voiding dysfunction
   e. Defecating dysfunction and/or fecal incontinence
7) QOL
   a. Global: SF-36 total scores and physical and mental sub-scale scores[13]
   b. Disease-specific: urinary, bowel and prolapse scales of PFIQ score[10]

Safety

8) Long-term adverse events specific to the surgical procedure:
   a. Vaginal granulation tissue, suture erosion or mesh exposure /erosion requiring treatment
   b. Vaginal or perineal stricture (i.e., narrowing or scarring) prompting a treating physician to suggest, or the subject to request, treatment (surgical or non-surgical)

D2. PMT Intervention

D2.1 *Primary outcome*

The primary outcome of the PMT intervention will be the development of prolapse symptoms as measured by the POPDI subscale of the PFDI and anatomic outcomes assessed up to 5 years after surgery. The primary anatomic outcome is identically defined to the primary anatomic outcome described for the surgical intervention (D.1) and assessed as time to failure.

D2.2 Secondary outcome measures

Outcome measures labeled with (*) are identical to those listed in D.1.2 for the Surgical Intervention; this does not represent additional data collection, rather the impact of perioperative PMT on these outcomes will be assessed independent of the surgical intervention consistent with the study's factorial design.

1) The anatomic outcomes of each vaginal segment (anterior, posterior, and apical) assessed by their corresponding POPQ point (Ba, Bp, and C, respectively) measured as a continuous variables*
2) Urinary incontinence (Hunskaar Incontinence Severity Index) at 3-5 years after surgery*[11]
3) Change in Urinary and colorectal symptoms from baseline as assessed by the UDI and CRADI subscales.*
4) Global improvement in bladder function – Subjects will complete the Patient Global Impression of Improvement[12] at 3-5 years after surgery*
5) Reoperation for stress urinary incontinence annually at 3-5 years after surgery*
6) Postoperative treatment for overactive bladder symptoms including anti-cholinergic use, intravesical Botox® (botulinum toxin A) injection and neuromodulation short-term at 3-5 years after surgery.
7) QOL (PFIQ[10] and SF-36[13]) 3-5 years after surgery.*

8) Pelvic muscle strength as assessed by the Brink Scale long-term (3-5 years after surgery) [14]

D.3. Enrollment intervention

D.3.1 Primary outcome
The primary outcome for primary aim 4, the enrollment intervention, will be the proportion of eligible subjects who consent to enroll in E-OPTIMAL, and complete all 3 data collection events in year 3 of E-OPTIMAL follow-up (year 5 from enrollment in OPTIMAL).

D.3.2 Secondary outcomes

1) The proportion of patients who enroll in E-OPTIMAL
2) The proportion who complete follow-up at 3, 4 and 5 years after surgery
3) Total number of data collection events (clinic visits, site and QOL calls), number of in-person clinic visits, and number of QOL calls completed
4) Satisfaction with the study informed consent process
5) Study-level and personal-level motivation and barriers to enrollment in E-OPTIMAL

E. STUDY POPULATION

E1. Inclusion Criteria

1. Completion of the Year 2 OPTIMAL in-person visit

E2. Exclusion Criteria

1. Inability to provide informed consent.
2. Subjects who are long-term residents of a skilled nursing facility (that is, residency is not limited to short-term rehabilitation) at the time of enrollment into E-OPTIMAL. Note: Subjects unable to return for annual visits are not excluded as they can participate in the telephone interview. However, every attempt will be made to encourage in-person participation.

E3. Criteria for termination of participation

(Due to evidence or likelihood that the subject can no longer consent for herself)

1. Subjects 75 years and older that fail the telephone mini-mental status examination. If the participant gets 5 or more of the 10 items "incorrect" the interviewer says "thank you very much for your time, that completes the interview for today." In other words, the interviewer in no way implies to the participant that they did not "pass" a test to continue. The interviewer contacts the appropriate site coordinator immediately after the interview to let them know of the outcome.
2. Subjects younger than 75 who appear to have cognitive deficits during the quality of life telephone interview will be administered the mini-mental status examination; those who fail will be excluded from further participation. (Proxy respondents will not be used.) Subjects who appear to have cognitive deficits during the in-person visit or site telephone interview will be withdrawn from the study by the study coordinator.
3. Subjects who become long-term residents of a skilled nursing facility.

4. Withdrawal of consent. Verbal assent will be obtained prior to each telephone interview and each in-person visit.

Note: Subjects that are unable to complete telephone interviews (for example, because of hearing loss) may complete the interview portion of the survey in person, either at the site or in the home.

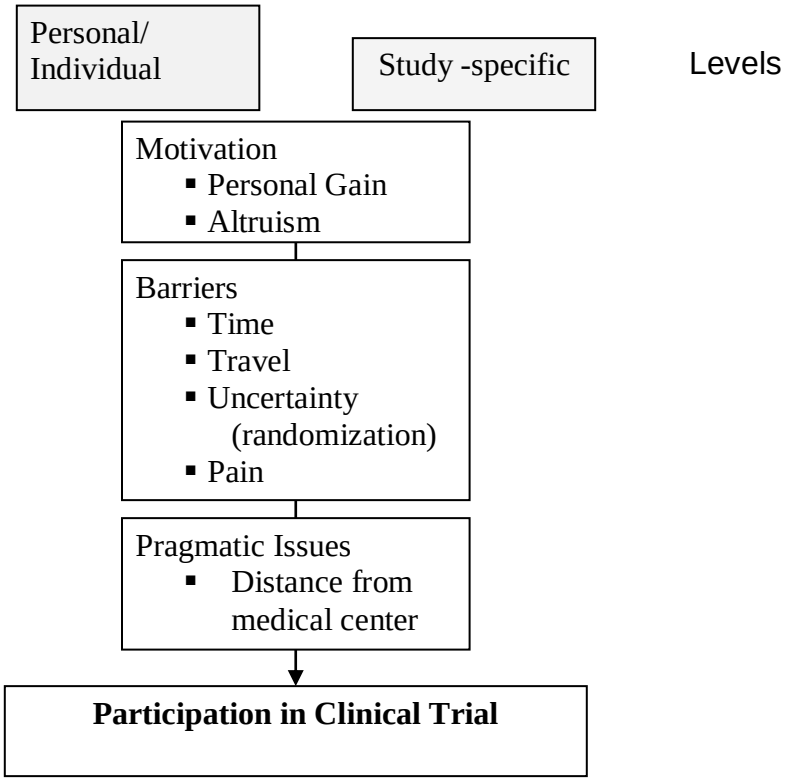
F. ENROLLMENT INTERVENTION

The enrollment intervention for E-OPTIMAL will compare two different informed consent processes. The control arm is the usual consent process, defined as the typical IRB approved informed consent process at each individual institution. The experimental arm is the viewing of a standardized video detailing the importance of long-term follow-up in studies of pelvic floor disorders followed by the usual consent process at each institution (Appendix H.C). Women randomized to the video arm will view the video and then have the standard discussion with the coordinator and sign consent. Participants will be unaware that recruitment is being studied. We have informally surveyed all participating IRBs and at this time, they agree that a waiver of consent is appropriate for this portion of the study.

F1. CONCEPTUAL FRAMEWORK

Little information is available in the literature on the factors that influence potential research subjects' willingness to participate in clinical trials. In order to provide guidance for the development of the enrollment intervention, a conceptual framework was developed based on the existing literature on this topic (summarized in section B. Background and Significance) as well as discussions with investigators experienced in recruiting and retaining participants in pelvic floor disorders. (Figure 1) In this framework, potential subjects consider three broad factors (motivation, barriers and pragmatic issues) at two levels (study level and personal/individual level) when deciding upon whether or not to participate in clinical trials. Motivation factors that may influence this decision can be separated into those that provide personal gain (e.g. monetary compensation; access to tests or treatment not available outside the study) and those that are altruistic (e.g. contribute to medical knowledge that may help others; help to make advances in medical research). Potential barriers or burdens that may be considered by a potential research subject include the extra time or travel required to participate, the uncertainty about which treatment they might receive, the pain or discomfort associated with study procedures and additional direct or indirect costs associated with study participation. Pragmatic factors which may have influence might include distance from the medical center, or easy access to transportation. Within this framework, a potential research subject will consider these factors based on their individual situation or perspective. Evaluated from this level, multiple factors would be expected to influence a subject's inclination to participate in research globally, including the flexibility of their schedule, general attitudes about research participation, access to transportation, etc. Potential study subjects will also consider these factors as they apply to a specific study and when considering whether or not to participate in a clinical trial including the specific treatments under study, the nature and number of study visits, the discomfort or risk of study procedures, etc.

Figure 1. Conceptual Framework for Enrollment and Retention Aim



This conceptual framework was used to guide the development of the video in the enrollment intervention. Specifically, it was felt that this medium had the potential to impact motivation factors both from the individual and study perspective and to provide details to minimize some of the potential barriers to study participation. As such, the following discussion points were used in developing the video:

- General sentiment on importance of women's research
- Congratulate the patient for OPTIMAL study completion.
- Thank the patient for participation to-date in OPTIMAL. Recognize the significant time commitment that she has dedicated to this study.
- Reinforce that while 2-year outcomes after surgery give valuable information, to evaluate long-term sequelae of the surgical procedures and the additional pelvic floor therapy, even longer follow-up would be of great benefit.
- Outline specifically what continued participation in E-OPTIMAL means for the patient: annual site telephone follow-up calls, quality of life telephone calls, and in-person evaluations at the clinical site.

Additionally, the conceptual framework was used to develop the Participants' perception of motivation and barriers to continued study participation questionnaire as outlined in H.3.e and Appendix B.

F2. ENROLLMENT PROCESS

At the final 2-year visit in OPTIMAL, potential participants in E-OPTIMAL will be randomized with equal probability to one of the intervention groups described above. This randomization occurs prior to initiating the E-OPTIMAL informed consent process in order to investigate the utility of the intervention in an unbiased manner since subject knowledge that the informed consent process is being studied may affect their participation in E-OPTIMAL (an outcome of interest). IRB approval for this "silent" randomization will be secured at all sites before potential subjects are approached in the OPTIMAL study. This randomized enrollment intervention represents negligible risk to participants.

The flow of the E-OPTIMAL enrollment process will be as follows:

1) , All OPTIMAL subjects will complete a questionnaire on motivation and barriers for participation in research (Appendix B) at the 24 month QOL interview, before being invited to participate in E-OPTIMAL at the 24 month in person OPTIMAL visit.
2) After completing all the OPTIMAL 24 month assessments,the study coordinator will randomize the subject in an area separate from the patient to determine the enrollment intervention assignment(video or no video) prior to the start of recruitment efforts to the extended study. The participant will not be informed of this randomization.
3) <u>If assigned to standard informed consent process</u>: after collecting the required research data for the OPTIMAL visit and the motivation and barriers questionnaire, the coordinator will inform the subjects that we are inviting OPTIMAL subjects to consider continuing follow-up for 3 more years as part of E-OPTIMAL. If the participant is interested in hearing more about the study extension, the study coordinators will then perform the usual informed consent process that is standard for their site.
4) <u>If assigned to the video intervention</u>: after collecting the required research data for the OPTIMAL visit and the motivation and barriers questionnaire, the coordinator will inform the subjects that we are inviting OPTIMAL subjects to consider continuing follow-up for 3 more years as part of E-OPTIMAL and invite them to view the study video. If willing, the subjects will then observe the video without the study coordinator present. The study coordinators will then go through the usual informed consent process that is standard for their site.

F3. RANDOMIZATION AND BLINDING

Randomization will be stratified by site with separate randomization schedules generated by the DCC using random permuted blocks. Subjects will be blinded to treatment assignment. Subjects will be unaware of the recruitment aim of this study. The study coordinator will not be blinded to the enrollment intervention. Evaluators of outcome assessments will remain masked to surgical, PMT, and enrollment process randomizations. Masking of the randomized OPTIMAL interventions will continue until all E-OPTIMAL subjects have completed the study and the database is locked.

G. FOLLOW-UP INTERVALS

1. In-person evaluation at the clinical site: annually, postoperative years 3-5 after OPTIMAL index surgery. Examinations will be done within three months before or after the anniversary of the initial surgery.
2. Site telephone follow-up (limited call to inquire about re-operation, change of address): approximately six months after the anniversary of the initial surgery and yearly thereafter (to fall approximately at the midpoint between annual assessments).
3. Quality of life telephone interviews by the central facility at the Data Coordinating Center: annually years 3-5 postoperatively within three months before or after the anniversary of the initial surgery.

H. MEASUREMENT

1. Yearly clinic visit
   Objective follow-up will be performed by research staff "masked" to surgical intervention group and will include:
   a. POP-Q for prolapse staging. The pelvic organ prolapse evaluation will be performed according to the guidelines established by the International Continence Society.[9] The procedure will be standardized as demonstrated in a videotape produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Examination"). Examinations will be performed in the dorsal lithotomy position with the subject straining maximally. Subjects will be asked to confirm that the extent of prolapse demonstrated during the examination is consistent with the maximum degree of prolapse seen in their daily life. Standing POPQ examinations will be performed if maximal prolapse cannot be demonstrated in the dorsal lithotomy position;
   b. Assessment of pelvic muscles. The pelvic muscles will be assessed using the Brink scale, a widely used standardized measure of pelvic muscle function with good inter- and intra-rater reliability.[14] The Brink scale assesses the pelvic muscles by rating three categories: contraction pressure, duration on squeeze, and displacement of the examiner's finger, each on a scale of 0-4, for an overall score of 0-12. The Brink assessment will be performed as described in the original article. The examiner will insert the index and middle finger approximately 4 to 6 cm into the vaginal canal and rotate them to assume a vertical position (index finger resting on top of the middle finger). The subject will be asked to contract her pelvic muscles a single time with the statement "Now I want you to squeeze your pelvic muscles for as long as you can as though you were trying to hold in gas." The examiner then scores the contraction based upon pre-defined criteria[14] ;
   c. Speculum examination to assess for suture or mesh erosion;
   d. Weight, height;
   e. Review of operative notes for re-operations related to pelvic floor dysfunction or complications of such surgeries;
   f. Review of re-treatments for urinary symptoms
   g. Interval treatment for pelvic floor disorders.
   h. Annual assessment of participants' perception of motivation and barriers to continued study participation. (Appendix B)

i. If patients have not completed the yearly QOL phone interview, the site will administer the POPDI subscale of the PFDI as this is necessary for the primary outcomes D1.1 and D2.1)

Re-operation information will be abstracted from review of medical records and operative notes. In cases where the surgery is performed outside the clinical sites of the PFDN, the subject will be asked by the site research coordinator to complete a release of information form for records pertaining to the pre-operative evaluation and the surgery itself.

2. Yearly telephone interview: In subjects who are unable/unwilling to present for annual site visits, the site research coordinator will contact the subject to query:
   a. Re-operation rates
      i. Re-operation for complications
      ii. Re-operation for prolapse
      iii. Re-operation for stress urinary incontinence (includes periurethral bulking injections)
   b. Non-surgical treatment for pelvic floor disorders
      i. Pessary use for prolapse
      ii. Stress urinary incontinence
      iii. Urge urinary incontinence and other overactive bladder symptoms
      iv. Voiding dysfunction
      v. Defecating dysfunction and/or fecal incontinence
   c. Post-operative adverse events:
      The following specific adverse events will be assessed and reported:
      i. Vaginal granulation tissue, suture erosion or mesh erosion/exposure requiring treatment;
      ii. Vaginal or perineal stricture (i.e., narrowing or scarring) prompting a treating physician to suggest or the subject to request treatment (surgical or non-surgical)
   d. Treatment for POP or UI (e.g., pessaries, collagen injections, other);
   e. Medications for urinary symptoms

   The site coordinator will ask the patient to sign a release of records for pertinent information such as re-operation or treatment for negative outcomes.

3. Yearly Quality of life telephone interview by the QOL Interviewing Center at the Data Coordinating Center:
   a. Pelvic symptoms:
      i. Prolapse symptoms - as measured by the POPDI subscale of the PFDI.
      ii. Urinary function: as measured by UDI scores[10] of the PFDI to assess urinary function generally and Hunskaar Incontinence Severity Index[11] to assess the presence and severity of urinary incontinence specifically. Additionally, subjects will complete the Patients Global Impression of Improvement (PGI-I)[12] to assess global improvement of bladder function.
      iii. Bowel function: CRADI scores of the PFDI[10]
   b. QOL
      i. Global: SF-36 [13]

ii. Disease-specific: PFIQ[10]

c. Assent for continued participation (may be done during telephone interview scheduling call);
d. Short Portable Mental Status Questionnaire (SPMSQ) – if subject is aged 75 or older, or if younger than 75 years old with apparent cognitive deficits;
e. Participants' perception of motivation and barriers to continued study participation.(Appendix B)

Timeline of visits, events and data collection for OPTIMAL and E-OPTIMAL (Grayed)

	OPTIMAL													E-OPTIMAL		
	Base	**Surgery & Hosp.**	**2 wk**	**4-6 wk**	**8 wk***	**3 mo**	**6 mo**	**9 mo**	**12 mo**	**15 mo**	**18 mo**	**21 mo**	**24 mo**	**3 yrs**	**4 yrs**	**5 yrs**
Window	-2mo		**±1 wk**	**±0 wk**	**±1 wk**	**±1 wk**	**±2 wk**	**±1 mo**	**±1 mo**	**±1 mo**	**±1 mo**	**±1 mo**	**-2 mo +4 mo**	**±3 mo**	**±3 mo**	**±3 mo**
Informed Consent	X												X†			
Assent for participation														X	X	X
Demographics	X															
Medical History	X															
Medications /Treatments	X		X	X		X	X		X		X		X	X*	X*	X*
Urodynamics	PRN															
Physical examination w/ POPQ	X			X			X		X				X	X	X	X
Pelvic muscle strength	X						X		X				X	X	X	X
Randomization	PMT	SURG											± VIDEO†			
PMT visit	X		X	X	X	X										
SF-36	X		X				X		X				X	X	X	X
Telephone interview/QOL	X						X		X				X	X‡	X‡	X‡
Adverse events		PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN
Motivation and Barriers to Participation													X	X	X	X
Reasons for Participation & Satisfaction w/ IC process													X			
Short Portable Mental Status^														X^	X^	X^

†Informed consent & randomization for E-OPTIMAL study.

* Only medications/treatments for urinary symptoms will be assessed for E-OPTIMAL

POPQ, pelvic organ prolapse quantitation; PMT, pelvic muscle therapy; QOL, quality of life (‡in E-OPTIMAL, includes PFDI, PFIQ, Hunskaar, PGI-I, Note: If patients have not completed the yearly QOL phone interview the site will administer the POPDI subscale of the PFDI)

^Administered to subjects 75 or greater years old, or those younger than 75 years old with apparent cognitive deficits

I. DATA COLLECTION

All data collection will be performed by research staff other than the study surgeon. All research staff will be trained and certified to perform data collection procedures. Allowable windows for timed evaluations and telephone interviews include a three-month window on each side of the anniversary of the initial surgery and interim telephone call (by site research coordinator).

Data collected in this protocol will be merged with data collected in the OPTIMAL protocol for analysis.

Throughout the study, subject data will be collected by any of three methods: during a research office visit, during a telephone call from research staff and/or during a telephone interview by the QOL Interviewing Center

J. STATISTICAL AND DATA MANAGEMENT CONSIDERATIONS

J1. Sample size and Power

The OPTIMAL trial surgical intervention compares the surgical success (as defined above) as a dichotomous variable between SSLF and ULS 2 years after surgery. The estimated sample size for OPTIMAL is 340 randomized subjects (170 per surgical treatment group) to allow us to differentiate between success rates of 70% and 83% using a two-tailed 5% level of significance. A total of 400 subjects are expected to be enrolled (200 per group) to allow for a projected 15% drop out/loss to follow-up rate over 2 years.

The experience of the CARE follow-up study, E-CARE, provides some guidance on recruitment and retention parameters for studies that offer long-term follow-up after a randomized controlled clinical trial. In E-CARE, enrollment began when the subjects first enrolled in CARE reached their 2-year postoperative visit. There were 262 women who were recruited 24 months previously at the participating sites, and of these, 215 enrolled to E-CARE (82%). Dropout in E-CARE is 11% (17/149) for clinical visits and 13% (29/215) over 6 years (after randomization to CARE). Based on the PFDN experience with E-CARE, we conservatively assume that at least 75% of subjects in OPTIMAL (n=255) will enroll in E-OPTIMAL and that the annual drop-out/loss to follow-up rate will be approximately 5%. These assumptions would result in approximately 218 subjects providing year 5 data on E-OPTIMAL. If we further assume that recruitment and retention to E-OPTIMAL are balanced between the two surgical treatment arms, then we would have 109 subjects in each treatment group available for comparisons.

The primary endpoint for Aim 1 is time to surgical failure. Assuming time to surgical failure follows an exponential distribution and fixed follow-up on each subject for 5 years, there is 80% power to detect a hazard ratio of 0.52 (based on the 2-year surgical success rates of 83% and 70% in the ULS and SSLF arms, respectively) with a two-sided Type I error of 5% with only 167 subjects. Thus, there is a reasonable chance that a clinically relevant difference in time to surgical failure can be detected, if our assumptions are approximately true.

Similarly, clinically relevant differences in comparisons of continuous variables including POPQ measurements and HRQOL scores will likely also be detectable with this sample size. Assuming 218 subjects followed for 5 years with equal numbers in each treatment group, we would have

80% power to detect effect sizes of 0.38 in continuous outcomes with a two-sided Type I error of 5%. However, should enrollment in E-OPTIMAL be lower or attrition higher than expected, E-OPTIMAL will still provide valuable long-term prospective information about women undergoing vaginal reconstructive surgery and TVT for treatment of pelvic organ prolapse and stress urinary incontinence including long-term rates of reoperation, anatomic and symptomatic prolapse recurrence, recurrence of SUI, and long-term negative outcomes.

The primary end point for primary aim 4 is the proportion of subjects who consent to enroll in E-OPTIMAL and complete all 3 data collection events in year 3 of E-OPTIMAL follow-up (year 5 from enrollment in OPTIMAL). Power calculations for this aim are based on the PFDN experience with E-CARE. Assuming that the number of eligible women in OPTIMAL who enroll in E-OPTIMAL using the standard informed consent process is 75% and the annual loss to follow-up is 5%, then the proportion of subjects in the non-intervention enrollment group who enroll and complete 5 years of follow-up in E-OPTIMAL would be 64%. With N=340 (170/group), we have 87% power to detect a 15% difference between the enrollment interventions (64% vs. 79%) using a two-sided Type I error rate of 5% for aim 4. In our opinion, if the addition of the video to the informed consent process improved this proportion by 15% or more then this would be clinically important.

There is no adjustment of the experiment-wise Type I error for the two hypothesis tests (for aims 1 and 4), given that each aim is focused at different interventions (one from the original study and one from the extension study).

J2. Data Analysis

For E-OPTIMAL, the primary outcome will be time to surgical failure, with surgical failure defined in Section D1. The primary analysis approach will be Intent to Treat. The primary outcome and other time-to-event outcomes will be analyzed using appropriate methods, such as log-rank tests, Kaplan-Meier survival curve estimation, and proportional hazards models. Continuous and dichotomous data will be compared using general linear and logistic models, respectively, in a manner consistent with the current OPTIMAL statistical plan. The primary endpoint for the E-OPTIMAL enrollment intervention (primary aim 4) will be assessed using the Chi-square test.

J3. Data Management

The DCC maintains a website for data management. The website is password protected. All transmissions to and from the website are encrypted using SSL. In addition to providing access to the study database, the website contains the protocol, manual of operations, current versions of the case report forms and other information related to the study. As needed, the study coordinator prints blank case report forms from the website. An investigator and/or study coordinator can only view data in the study databases from his/her clinical site.
Select case report forms are completed and countersigned by the investigator or study coordinator. On the case report forms, a subject identification number that consists of a two-digit site number and a four-digit sequential identification number identify each subject. No other personal identification is included on case report forms that are submitted to the data coordinating center.

The original case report forms are securely maintained at the clinical sites. Clean copies of the case report forms are sent monthly to the DCC where they are entered into the study database using double entry (entry and verification). Forms, such as those containing serious adverse events, are entered by the coordinator directly into the study website; these forms are also sent monthly to the DCC and entered a second time for verification. Since the central QOL Interviewing Center must be able to contact the subject, contact information is entered by the coordinator using the study website into a second database that is not accessible to staff of the data coordinating center (other than the database developer), but is accessible to the QOL Interviewing Center; conversely, the staff of the QOL Interviewing Center do not have access to the research database.

J4. Recruitment Estimate/Attrition Estimate

Based on the PFDN experience with E-CARE, we assume that at least 75% of subjects in OPTIMAL (n=255) will enroll in E-OPTIMAL and that the annual drop-out/loss to follow-up rate will be approximately 5%. Based on the ages of women enrolled in OPTIMAL at baseline (as of May, 2009), the proportions of women in various age groups at the end of E-OPTIMAL (5 years after the baseline of OPTIMAL) are as follows:

Age, years	OPTIMAL (Actual, as of 1/26/2009) N=81	E-OPTIMAL (Projected) N= 218
>30 to ≤ 40	6 (7.4%)	8 (4%)
>40 to ≤ 50	15 (18.5%)	28 (13%)
>50 to ≤ 60	35 (43.2%)	67 (31%)
>60 to ≤ 70	17 (21.0%)	70 (32%)
>70 to ≤ 80	8 (9.9%)	34 (15%)
>80	0	11 (5%)

Thus, by the end of E-OPTIMAL, we estimate that 5% of the women will be over 80 years, and 12% will be over 75 years. Approximately 10% of those over age 75 will be expected to die, enter skilled nursing care, or develop dementia (thereby meeting our criteria for termination of participation). Therefore, we anticipate declining continuation rates as E-OPTIMAL progresses. However, we do not anticipate a large dropout rate for factors other than these exclusion criteria. Based on sample size calculations for the primary endpoints, we will still have sufficient women to evaluate outcomes.

K. ETHICAL CONCERNS

K1. Ethical Concerns

Currently these same patients receive treatment without the kind of follow-up that would allow us to be able to learn from their experience and, as a result, guide more effective clinical decisions. Their treatment will not be impacted by the E-OPTIMAL protocol.

Follow-up visits for E-OPTIMAL will be scheduled to coincide with regularly scheduled clinic appointments. For sites in which patients are generally NOT seen after 2 post-operative years, the subject will be made aware of the fact that the annual examinations are optional, and are part of a research study.

It is important to ensure that subjects are still capable of consenting for themselves for continued study participation. Given that some women will develop dementia during the progress of the trial, the telephone interviewers will administer the Short Portable Mental Status Questionnaire to all women ages 75 and older, and to those that appear to have cognitive dysfunction during the course of the interview. If the participant gets 5 or more of the 10 items "incorrect" the interviewer says "thank you very much for your time that completes the interview for today." In other words the interviewer in no way implies to the participant that they did not "pass" a test to continue. The interviewer contacts the appropriate site coordinator immediately after the interview to let them know of the outcome. Subjects who do not pass this cognitive assessment will be withdrawn from further study participation. This approach is consistent with that recommended by the American Psychiatry Association joint subcommittee on psychiatry and law (Am J Psychiatry 155: 11, November, 1998).

K2. Informed Consent

Subjects will be approached for enrollment into this follow-up study at their final (24 month) OPTIMAL visit. Written informed consent will be obtained at that time for all subjects. The consents will be subsequently updated at future visits depending on IRB or Federal requirements at that time. (See section F. for specifics regarding enrollment with informed consent intervention.) Additionally, half of all potential participants will view a video at the time of consent detailing the importance of long-term follow-up studies in pelvic floor disorders – see enrollment intervention.

At each visit, verbal assent will be obtained from subjects for continued participation in the study (either the entire study or one part only).

A common template for the informed consent form will be used by all of the centers, modifying the content or format as necessary to meet the requirements of their respective institutional human subjects committees.

K3. Risks

This follow-up study is primarily observational and does not involve any interventions or invasive procedures. A speculum examination will be done. While the aim of the examination is to quantify pelvic organ prolapse, the examination is not substantially different from a pelvic

examination done for routine care, and thus entails minimal, if any, discomfort. The subject's privacy will be protected as outlined in the data management section. Federal HIPAA rules will be complied with.

K4. Data Safety Monitoring Board

The National Institutes of Health have set up a Data Safety Monitoring Board (DSMB) to oversee this study. Members of the DSMB are independent of the study investigators and represent Urology, Urogynecology and Biostatistics, as well as having a lay member. The DSMB will meet every six months or more frequently if requested by the Chair, either in person or by teleconference. This protocol must be approved by the DSMB prior to implementation.

K5. Adverse Event Reporting

The E-OPTIMAL study is an observational extension of the original OPTIMAL protocol and does not involve a treatment intervention. A primary goal of E-OPTIMAL is to ascertain the long-term failure rates associated with either the sacrospinous ligament suspension or the uterosacral ligament suspension and TVT procedure. Therefore, negative outcomes that may be related to these procedures, as evidenced by treatments or re-operation for prolapse or incontinence, suture or mesh erosions, and periurethral implants for stress incontinence (such as collagen) will be collected by the Study Coordinator at the time of the yearly clinic or telephone visit and reported to the DSMB in summary format. Similarly, any additional pelvic (urologic, colorectal, and gynecological) surgery will be collected annually and reported to the DSMB in summary format. It should be noted that many of these diagnoses, procedures, and hospitalizations will be subsequently judged as not related to the SSLS or ULS but, to avoid underestimating long-term effects, these outcomes will be collected consistently and judged by the Adjudication Committee masked to the subjects' group assignment.

Outcomes that are not likely related to SSLS, ULS, or TVT (i.e., non-urologic/non-colorectal/non-gynecologic diagnoses, procedures and hospitalizations) will not be collected. By definition, as E-OPTIMAL starts two years after the randomization for the index surgery of OPTIMAL, fatalities will most likely not be reported as an outcome related to the SSLS or ULS.

Since the above outcomes will not be classified as serious adverse events, they will <u>not</u> be reported to the Safety Monitor or the DSMB or the IRB in an expedited manner.

L. RESEARCH COSTS

Subjects will be reimbursed the cost of transportation and parking for the site visits, in addition to compensation for their time. They will be compensated for their time for the site visits and telephone calls, at $50 for each clinical site visit and $25 for each quality of life telephone interview. Subjects will not be compensated for the brief interval telephone calls from the clinical sites.

N. REFERENCES

1. BARBER MD, BRUBAKER L, MENEFEE S, et al. Operations and pelvic muscle training in the management of apical support loss (OPTIMAL) trial: design and methods. Contemp Clin Trials 2009;30:178-89.
2. DIWADKAR GB, BARBER MD, FEINER B, MAHER C, JELOVSEK JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009;113:367-73.
3. BENSON JT, LUCENTE V, MCCLELLAN E. Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. Am J Obstet Gynecol 1996;175:1418-21; discussion 1421-2.
4. SILVA WA, PAULS RN, SEGAL JL, ROONEY CM, KLEEMAN SD, KARRAM MM. Uterosacral ligament vault suspension: five-year outcomes. Obstet Gynecol 2006;108:255-63.
5. PARAISO MF, BALLARD LA, WALTERS MD, LEE JC, MITCHINSON AR. Pelvic support defects and visceral and sexual function in women treated with sacrospinous ligament suspension and pelvic reconstruction. Am J Obstet Gynecol 1996;175:1423-30; discussion 1430-1.
6. RYAN RE, PRICTOR MJ, MCLAUGHLIN KJ, HILL SJ. Audio-visual presentation of information for informed consent for participation in clinical trials. Cochrane Database Syst Rev 2008:CD003717.
7. BENSON PR, ROTH LH, WINSLADE WJ. Informed consent in psychiatric research: preliminary findings from an ongoing investigation. Soc Sci Med 1985;20:1331-41.
8. WESTON J, HANNAH M, DOWNES J. Evaluating the benefits of a patient information video during the informed consent process. Patient Educ Couns 1997;30:239-45.
9. BUMP RC, MATTIASSON A, BO K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-7.
10. BARBER MD, KUCHIBHATLA MN, PIEPER CF, BUMP RC. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. Am J Obstet Gynecol 2001;185:1388-95.
11. SANDVIK H, SEIM A, VANVIK A, HUNSKAAR S. A severity index for epidemiological surveys of female urinary incontinence: comparison with 48-hour pad-weighing tests. Neurourol Urodyn 2000;19:137-45.
12. YALCIN I, BUMP RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003;189:98-101.
13. WARE JE, JR., SHERBOURNE CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
14. BRINK CA, WELLS TJ, SAMPSELLE CM, TAILLIE ER, MAYER R. A digital test for pelvic muscle strength in women with urinary incontinence. Nurs Res 1994;43:352-6.
15. MORLEY GW, DELANCEY JO. Sacrospinous ligament fixation for eversion of the vagina. Am J Obstet Gynecol 1988;158:872-81.
16. IMPARATO E, ASPESI G, ROVETTA E, PRESTI M. Surgical management and prevention of vaginal vault prolapse. Surg Gynecol Obstet 1992;175:233-7.
17. SHULL BL, CAPEN CV, RIGGS MW, KUEHL TJ. Preoperative and postoperative analysis of site-specific pelvic support defects in 81 women treated with sacrospinous ligament suspension and pelvic reconstruction. Am J Obstet Gynecol 1992;166:1764-8; discussion 1768-71.
18. PASLEY WW. Sacrospinous suspension: a local practitioner's experience. Am J Obstet Gynecol 1995;173:440-5; discussion 445-8.
19. PENALVER M, MEKKI Y, LAFFERTY H, ESCOBAR M, ANGIOLI R. Should sacrospinous ligament fixation for the management of pelvic support defects be part of a residency program procedure? The University of Miami experience. Am J Obstet Gynecol 1998;178:326-9.

20. COLOMBO M, MILANI R. Sacrospinous ligament fixation and modified McCall culdoplasty during vaginal hysterectomy for advanced uterovaginal prolapse. Am J Obstet Gynecol 1998;179:13-20.
21. MESCHIA M, BRUSCHI F, AMICARELLI F, PIFAROTTI P, MARCHINI M, CROSIGNANI PG. The sacrospinous vaginal vault suspension: Critical analysis of outcomes. Int Urogynecol J Pelvic Floor Dysfunct 1999;10:155-9.
22. SZE EH, KOHLI N, MIKLOS JR, ROAT T, KARRAM MM. A retrospective comparison of abdominal sacrocolpopexy with Burch colposuspension versus sacrospinous fixation with transvaginal needle suspension for the management of vaginal vault prolapse and coexisting stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1999;10:390-3.
23. LANTZSCH T, GOEPEL C, WOLTERS M, KOELBL H, METHFESSEL HD. Sacrospinous ligament fixation for vaginal vault prolapse. Arch Gynecol Obstet 2001;265:21-5.
24. MAHER CF, QATAWNEH AM, DWYER PL, CAREY MP, CORNISH A, SCHLUTER PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol 2004;190:20-6.
25. JENKINS VR, 2ND. Uterosacral ligament fixation for vaginal vault suspension in uterine and vaginal vault prolapse. Am J Obstet Gynecol 1997;177:1337-43; discussion 1343-4.
26. COMITER CV, VASAVADA SP, RAZ S. Transvaginal culdosuspension: technique and results. Urology 1999;54:819-22.
27. BARBER MD, VISCO AG, WEIDNER AC, AMUNDSEN CL, BUMP RC. Bilateral uterosacral ligament vaginal vault suspension with site-specific endopelvic fascia defect repair for treatment of pelvic organ prolapse. Am J Obstet Gynecol 2000;183:1402-10; discussion 1410-1.
28. KARRAM M, GOLDWASSER S, KLEEMAN S, STEELE A, VASSALLO B, WALSH P. High uterosacral vaginal vault suspension with fascial reconstruction for vaginal repair of enterocele and vaginal vault prolapse. Am J Obstet Gynecol 2001;185:1339-42; discussion 1342-3.
29. SHULL BL, BACHOFEN C, COATES KW, KUEHL TJ. A transvaginal approach to repair of apical and other associated sites of pelvic organ prolapse with uterosacral ligaments. Am J Obstet Gynecol 2000;183:1365-73; discussion 1373-4.
30. AMUNDSEN CL, FLYNN BJ, WEBSTER GD. Anatomical correction of vaginal vault prolapse by uterosacral ligament fixation in women who also require a pubovaginal sling. J Urol 2003;169:1770-4.
31. SANDVIK H, HUNSKAAR S, SEIM A, HERMSTAD R, VANVIK A, BRATT H. Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey. J Epidemiol Community Health 1993;47:497-9.

Appendix A: List of Questionnaires

1. Pelvic Floor Distress Inventory (PFDI)[10]
2. Pelvic Floor Impact Questionnaire (PFIQ)[10]
3. Hunskaar Incontinence Severity Index[31]
4. Patient Global Impression of Improvement (PGI-I)[12]
5. SF-36[13]
6. Short Portable Mental Status Questionnaire (75 or older or if cognitively impaired)
7. Participants' Perception of Motivation and Barriers to Continued Study Participation
8. Reasons for Participating in E-OPTIMAL & Satisfaction with Informed Consent Process

Appendix B: Participants' Perception of Motivation and Barriers to Continued Study Participation

1. Please rank the three most important reasons that you participate in women's health research. (Provide a rank of 1 most important, 2 second most important, 3 third most important)

____I enjoy making contributions to medical research
____I want to contribute to medical knowledge that may help others, including my loved ones, in the future
____I want to improve my own health
____I think that studies improve my own access to a specific medical test or treatment
____I think that health care is better for research participants
____I want the extra money or incentives (for example, gifts)
____Other reason: _____

2. Please rank the three most important reasons that you participated in the OPTIMAL study. (Provide a rank of 1 most important, 2 second most important, 3 third most important)

_____I enjoyed making contributions to the OPTIMAL study because it advances medical research
____ I wanted to contribute to the OPTIMAL study because I believe that the OPTIMAL study may help others, including my loved ones, in the future
____I believe that participation in the OPTIMAL study would improve my own health
____I thought that the OPTIMAL study improved my own access to specific medical treatment, such as physical therapy
____I thought that health care is better for research participants in the OPTIMAL study as compared to women who did not participate
____I wanted the extra money or incentives that are part of the OPTIMAL study
____Other reason: _____

3. What are the most important ways for your research team to show their appreciation to you for your contributions to the study?

	Very Important	Important	Neither Important nor Unimportant	Unimportant	Very Unimportant
Money					
Less waiting time for your appointment					
Gifts					
Share results of study					
Free parking					
Verbal appreciation					
Other factor: _____					

4. For each of these following items, please indicate whether these affect your decision to participate in a research study?

	Very Important	Important	Neither Important nor Unimportant	Unimportant	Very Unimportant
Pain or discomfort involved for study procedures					
Extra time involved for study					
Travel time or distance					
Travel costs					
Uncertainty about which treatment you'll receive (randomization)					
Difficulty scheduling visits (for example, taking time off from work, other activities)					
Not enough money					
Not enough gifts or other reward (not including money)					
Family care responsibilities (for spouse, parent or child)					
□ Other factor: _____					

5. Typically, how do you get to your clinical research visits? (Choose only one answer)

- □ Drive your own car
- □ Take public transportation
- □ Walk
- □ Family Member drives you
- □ Friend drives you
- □ Other: _____

6. Typically, how long does it take you to travel to your OPTIMAL clinical research visits? (Choose only one answer)

- □ less than 15 minutes
- □ 15 minutes to less than 30 minutes
- □ 30 minutes to less than 1 hour
- □ 1 hour or greater

7. Please rank your top three preferences for ways to answer questions about your health in a study. (Provide a rank of 1 most preferred, 2 second most preferred, 3 third most preferred).

___ clinic visit
___ telephone interview
___ internet questionnaire
___ mail-in questionnaire
___ other: _____

Appendix C: Reasons for Participating in E-OPTIMAL & Satisfaction with Informed Consent Process

On behalf of the many women affected by pelvic floor disorders, thank you for volunteering to participate in the E-OPTIMAL study and continue the research visits and phone interviews that you started in the OPTIMAL study for three more years.

We are interested in better understanding the factors that played a role in your decision to volunteer to participate in E-OPTIMAL. It is important to note that the answers you provide in this survey will not be shared with your surgeon or study coordinator.

1. Please rate the importance of each of the following factors in your decision to participate in this three year extension of the OPTIMAL study:

	Very Important	Important	Neither Important or Unimportant	Unimportant	Very Unimportant
The verbal information provided to you about the study from your surgeon					
The verbal information provided to you about the study from the research coordinator/study nurse					
The written information provided to you about the study					
The information provided to you in the video about the study					
The information provided to you on the web about the study					
Your relationship with your surgeon					
Your relationship with the research coordinator/study nurse					

2. Please circle one response for each of the following items:

		Strongly Agree	Agree	Disagree	Strongly Disagree
a.	I feel well informed about the E-OPTIMAL study.	1	2	3	4
b.	The purpose of the study was well explained to me.	1	2	3	4
c.	The nature and extent of the study visits and phone calls were well explained to me.	1	2	3	4
d.	The expected duration of the study was well explained to me.	1	2	3	4
e.	The potential risks of study participation were well explained to me.	1	2	3	4
f.	The potential benefits *to society* of study participation were well explained.	1	2	3	4
g.	The potential benefits *to me* of study participation were well explained.	1	2	3	4

3. Overall, how satisfied are you about the information you received about the E-OPTIMAL study?

A. Very Satisfied
B. Somewhat Satisfied
C. Neither Satisfied or Dissatisfied
D. Somewhat Dissatisfied
E. Very Dissatisfied

Appendix D: Enrollment Intervention Video Script (detailing the importance of long-term follow- up in studies of pelvic floor disorders)

Thank you for your past contributions to women's pelvic health research. As you may know, pelvic floor disorders such as pelvic organ prolapse and urinary incontinence are common, affecting approximately 23% of American women. About one in ten between the ages of 20 and 39 years are affected and with aging, even more women develop these disorders. Unfortunately, due to a lack of research, many women are treated without the benefit of high quality information about the best treatments.

The federally funded Pelvic Floor Disorders Network, or PFDN, conducts women's health studies that provide the most up-to-date information so that all women with pelvic floor disorders can be treated in the best possible way. We know that clinical studies increase awareness about pelvic floor disorders and improve care for women across our nation, so that more women are given the best treatments for these common problems. It is vital that everyone including physicians, nurses, and patients alike have this information to make the best possible informed decision when it comes to their care.

We recognize that women like you who participate in clinical research are special partners in women's health research. Participation of women like you in research has advanced our knowledge on the treatment of conditions such as breast cancer and heart disease. Major improvements in breast cancer treatment are a great example of the amazing benefits research can bring to women's health care – and advances in breast cancer care show the importance of extended or long-term research participation. Compared to 35 years ago, a woman has a better chance of surviving her breast cancer because of improved detection as well as more effective treatments. Similarly, long-term follow-up has improved the detection and treatment of heart disease in women.

We want to acknowledge and thank you for your own contribution to women's health research. You are one of the many participants who have contributed your time to the OPTIMAL study – by completing surveys, talking with research nurses, and doctor visits. It has been about 2 years since your reconstructive pelvic surgery and the start of your participation in the "OPTIMAL" study. The results from your surveys and exams will be critical as researchers study the most effective and safest ways to help women like you with problems such as urinary incontinence and pelvic organ prolapse.

Before your surgery two years ago, you may have asked your doctor "how many years will this surgery last"? Doctors and patients alike want to know this, but there has not been much research to answer this question. Most studies stop checking patients soon after their prolapse surgeries. But we know that when we follow patients longer, we can make important discoveries about the success of her particular procedure as well as determining if pelvic muscle exercises contributed to that success.

We would like you to consider joining with other OPTIMAL participants in continued participation in the extended OPTIMAL trial. This extension will last another three years which will help us learn how successful your surgery will be up to 5 years after your surgery. We are asking continuing participants to return for an annual physical examination once a year for three more years. In addition, we ask that you continue to participate in an annual telephone call to update us about any changes in your health and to assess your quality of life. The research nurse coordinator will be happy to give you additional information about the extended version of this study and review a consent form about your continued participation in the study.

We sincerely appreciate your completion of the OPTIMAL study. We hope that you have benefited from your participation in this important research and that you will join the other women who will continue participation in the extended study over the coming few years. Your participation is essential to help all of us deliver the best care available to all women whose life is impacted by pelvic floor disorders. We look forward to working together with you as an essential member of our team to meet this worthy goal. Thank you.