Urinary Incontinence Treatment Network

Study Protocol:
A Randomized Clinical Trial of the Burch Modified Tanagho and Autologous Fascia Sling Procedures

September 30, 2002

TABLE OF CONTENTS

APPENDICES

FIGURES AND TABLES

INTRODUCTION

The **U**rinary **I**ncontinence **T**reatment **N**etwork **(UITN)** is a consortium of Investigators from nine Continence Treatment Centers (CTC) and a Biostatistical Coordinating Center (BCC). The primary goal of the UITN is to assess the long-term outcomes of the most commonly applied treatments for women with the diagnosis of stress and mixed urinary incontinence. The UITN is supported by cooperative agreements from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with the National Institute of Child Health and Human Development (NICHD).

The **Continence Treatment Centers** are:

- University of Alabama - Birmingham, Alabama
- University of California - San Diego, California
- University of Maryland - Baltimore, Maryland
- University of Pittsburgh - Pittsburgh, Pennsylvania
- University of Texas - Dallas, Texas
- University of Texas - San Antonio, Texas
- University of Utah - Salt Lake City, Utah
- Beaumont Hospital - Royal Oak, Michigan
- Loyola University - Chicago, Illinois

The **Biostatistical Coordinating Center** is:

- New England Research Institutes - Watertown, Massachusetts

The **NIH Project Scientists** are:

- NIDDK: Leroy Nyberg, MD, PhD
  John Kusek, PhD
- NICHD: Anne Weber, MD, MS

Steering and Planning Committee

The primary governing body of the study is the Steering and Planning Committee comprised of each of the Principal Investigators of the CTCs and the BCC, the Chairperson of the Steering and Planning Committee, and the NIH Project Scientists. The Steering and Planning Committee will, in addition to developing the study protocol, propose interim and final data analysis plans, and, along with their staff at the CTCs, recruit, perform surgery, provide pharmacological and behavioral therapy, and provide follow-up for study participants. The members of the Steering and Planning Committee will serve as chairs of the various sub-committees of the UITN. The Steering and Planning Committee is chaired by William Steers, MD, University of Virginia.

Executive Committee

The Executive Committee includes the Chairperson of the Steering and Planning Committee, the Principal Investigator of the BCC, NIH Project Scientists, and when necessary, Chairpersons of the various sub-committees of the Steering and Planning Committee. The purpose of this committee is to handle problems that arise during the interim of regularly scheduled Steering and Planning Committee meetings.

External Advisors/Data Safety and Monitoring Board

An independent group of experts in urology, urogynecology, biostatistics, clinical trials, behavioral medicine, nursing, and ethics who are not otherwise involved in the study has been appointed by the NIDDK to review periodically the progress of the study. Such monitoring will include at least the following: review of study protocols prior to implementation; monitoring of patient accrual; review of reported adverse events; monitoring of protocol compliance; review of data analysis plans; monitoring data quality, and interim monitoring of study endpoints.

PROTOCOL

A. STUDY AIMS

The primary aim of this randomized clinical trial is to compare the Burch modified Tanagho and autologous fascia sling procedures for overall treatment success and stress-related symptoms at a minimum of 24-months post-surgery in women with predominant stress incontinence.

The secondary aims of the trial are:

- to compare complications including voiding dysfunction, quality of life, sexual function, satisfaction with treatment outcome, and need for additional surgery or other postoperative treatment for the two surgical procedures;
- to determine the prognostic value of urodynamic studies and to identify urodynamic parameters that predict treatment success in each surgical procedure.

B. BACKGROUND AND SIGNIFICANCE

B.1 Urinary Incontinence: Prevalence and Impact

Of the estimated 16 million Americans who suffer from urinary incontinence (Fantl, Newman, Colling, & al, 1996), two-thirds are women. Individuals with incontinence suffer social isolation, sexual and relationship dysfunction, and depression (Hunskaar & Vinsnes, 1991). The monetary cost to society is over $26 billion annually; most of this money is spent on the consequences of incontinence, not on its treatment (Wagner & Hu, 1998). Urinary incontinence remains an under-reported and under-treated condition. Patients suffer in silence because they think incontinence is a normal part of aging, or they feel embarrassed to discuss the problem with their physician (Norton, MacDonald, Stanton, & Sedgwick, 1988). In spite of these staggering statistics, there have been surprisingly few rigorously conducted scientific studies on the epidemiology, etiology or treatment of incontinence. The field suffers from a general lack of uniformity and standardization in the incontinence literature.

Stress urinary incontinence (SUI) is the most common type of urinary incontinence in women. It is estimated that upwards of 80% (Burgio, Matthewss, & Engel, 1991) of women suffering from urinary incontinence have a component of SUI. Most SUI results from bladder neck hypermobility (BNHM) with incomplete transmission of pressure to the urethra so that bladder pressure exceeds urethral pressure at the instant of a physical stress. Most women with SUI also have decreased intrinsic urethral resistance; if this deficit reaches critical levels and is a major cause of SUI, the condition is termed intrinsic sphincter deficiency (ISD). ISD is often seen with more severe SUI clinically. BNHM and ISD can coexist and can be masked by pelvic organ prolapse (POP). There are numerous therapeutic options for the treatment of SUI ranging from behavioral therapy to surgical therapy. The options presented to the patient vary by region, specialty, and individual practitioner. Treatment alternatives depend on the etiology of the incontinence, the patient's desires and very often the physician's experience.

B.2 Current Status of Surgical Outcome Studies in Female Urinary Incontinence

A woman's lifetime risk of surgery for SUI or POP is 11%, with nearly one-third of surgeries being performed for recurrences (Olsen, Smith, & Bergstrom, 1997). A large number of procedures have been developed to correct BNHM and ISD, and a partial list of these procedures includes anterior colporrhaphy, needle urethropexy, retropubic procedures (Burch

colposuspension and Marshall-Marchetti-Krantz procedure), sling procedures, bulking agents, and artificial sphincters. Most of these procedures are directed at correction of BNHM; bulking agents, slings, and artificial sphincters are directed at ISD or combined BNHM/ISD.

Most of the literature describing the results of the above-mentioned procedures does not meet contemporary standards for outcomes analysis. The 1996 Clinical Practice Guidelines in Urinary Incontinence (Fantl et al., 1996), issued by the Agency for Health Care Policy and Research (AHCPR), concluded that the surgical literature was deficient "in describing the patient population, the type of incontinence, the methods for accurate diagnosis, the techniques of the surgical procedure, or the outcome in different domains." Two other major reviews substantiate these findings. Black and Downs' (1996) exhaustive review of the surgical literature documents the extant methodological flaws including variability of case definition, failure to account for known confounders, lack of standardization of technique, variability in duration of follow-up, poor generalizability, inadequate power to detect clinically important differences, lack of assessment of complications, and marked variability in outcome assessment. The American Urologic Association (AUA) in 1996 undertook a comprehensive review of relevant surgical procedures, and this organization similarly concluded that most studies did not contribute to our understanding of the problem of incontinence, which evaluations were meaningful, and how a cure is defined clinically (Leach et al., 1997).

B.3 Comparison of the Important Anti-Incontinence Procedures: Rationale for Comparison of Burch and Sling Procedures

Acknowledging the limitations of the surgical literature reviews, the AUA review and the analysis by Black and Downs (1996) reached similar conclusions: 1) The Burch colposuspension appears to be more effective than anterior colporrhaphy in the treatment of SUI. Both reviews reported consistent cure rates of 85-90% for the Burch compared to 50-70% for the anterior colporrhaphy. Durability with the Burch seems good (82-90% at 5-8 years) while the anterior colporrhaphy has intermediate results which are more disappointing than the short term results, ranging from 37 to 84% continent rates (Jarvis et al., 1999). 2) The Burch colposuspension appears to be more effective than the needle suspension (modified Pereyra, Stamey, Raz) in the treatment of SUI. Here again, the continence rates are reported as 85% for the Burch and 50-70% for the needle suspensions in general, with the durability of the needle suspension being notably poor. 3) The Burch colposuspension and pubovaginal sling have similar cure rates.

Comparisons and contrasts between the Burch colposuspension and the pubovaginal sling are more subtle. First, the success rates reported for the pubovaginal sling are similar to those reported for the Burch, with one important difference: the sling has traditionally been reserved for patients undergoing secondary procedures. It has been argued that higher success rates for the sling might be seen if the sling would be promoted for use in primary cases. The WHO-sponsored International Consultation on Incontinence (Jarvis et al., 1999) compared the three randomized trials and one prospective trial of the pubovaginal sling and Burch colposuspension procedures, and concluded that the success rates for these procedures were equivalent, although only one of the studies reported the randomized comparison as a primary operation (Lalos, Burglund, & Bjerle, 1993). These prospective studies suffer from small numbers (see Table 1), while the dozen retrospective studies have considerable methodological problems. One study by Iosif (1983) found a higher cure rate for the Burch (95%, 95%CI 91-98%) compared to pubovaginal sling (79%, 95%CI 72-85%).

Table 1: Sling vs. Burch Colposuspension*

	Sling		Burch	
	n	dry n	n	dry n
(Henriksson, 1978)	15	15	15	15
(Lalos et al., 1993)	14	11	22	17
(Enzelsberger, 1996)	36	33	36	31
(Richmond, 1989)	14	9	15	12
		86%		85%

*Summary from the Female Surgical Treatment group from the WHO First International Consultation on Incontinence, Jarvis et al (1999)

It has been suggested that complications, including voiding dysfunction and detrusor instability, are higher with the sling procedure (Ostergard, 1997). Two comparative studies have conflicting conclusions with respect to the complications of these two procedures. In women undergoing secondary procedures, Enzelberger and colleagues (1996) found a 13% incidence of *de novo* voiding dysfunction after sling procedures but not Burch procedures, while Marinkovic and colleagues (1998) found that there were fewer immediate complications associated with the pubovaginal sling compared to the Burch colposuspension (42% Burch versus 26% sling). Although the Burch seems to be a durable procedure after five and even ten years, there are few data on the durability of the pubovaginal sling, especially as a primary procedure.

This randomized clinical trial of the Burch modified Tanagho vs. the autologous fascia sling procedures compares outcomes beyond cure, such as post-operative voiding dysfunction, de novo detrusor instability, hospitalization time, recovery time, and quality of life. The prognostic value of pre-operative urodynamic testing (which has never been demonstrated prospectively) and identification of urodynamic parameters which predict surgical success will also be investigated. The importance of these secondary outcomes is illustrated by a recent decision analysis by Weber and Walters (2000). They compared the effectiveness and cost of Burch colposuspension and sling procedures for primary surgical treatment of genuine SUI in women. Exploring the clinical belief that the increased success rates for slings are associated with higher complication rates, these Investigators decided that the two procedures were equivalent in overall effectiveness, but that complications of retention and de novo detrusor instability did influence the decision analysis. Using estimates of outcomes and complications from mostly clinical series and some estimates from expert opinion, they concluded that the Burch colposuspension was the superior procedure when the risk of retention after sling was higher than 9.0%, or when the risk of de novo detrusor instability after sling was higher than 10.3%. The pubovaginal sling was superior when the risk of de novo detrusor instability after Burch was higher than 6.8%. The authors recommended that until a randomized clinical trial can be accomplished, individual surgeons should consider their complication rates when deciding on which procedure to use.

Tension-free vaginal tape (TVT) is a newer procedure that has experienced recent commercial success in Europe and the United States. A review of this procedure was presented by the manufacturer at the July 2001 International Consultation on Incontinence, and fewer than 200 cases were presented for long-term (i.e. five year) follow-up. Thus, the data are considered

too preliminary and the experience too recent to include TVT in a randomized trial at the present time.

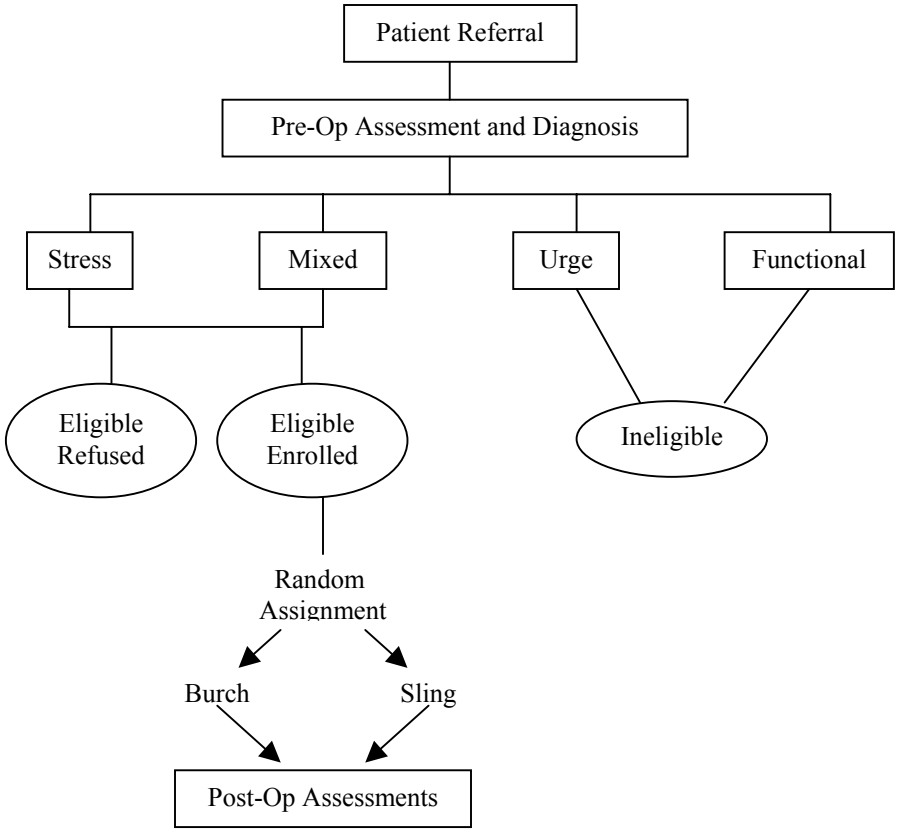
B.4 Advantages of a Randomized Clinical Trial

The fact that surgical trials in incontinence have failed to meet contemporary standards for outcome analysis highlights the difficulty in accomplishing these studies, especially when multicenter trials are needed to ensure adequate statistical power of the study. A randomized clinical trial will provide the best scientific evidence for answering the question of relative efficacy of the Burch modified Tanagho and autologous fascia sling procedures. This design will eliminate the confounding factors introduced by strong surgeon and patient preferences, and different patient populations and referral patterns at the different clinical centers. These factors would be very difficult to measure and adjust for in a non-randomized observational treatment comparison.

C. STUDY SCHEMA

The design of the trial is depicted in Figure 1.

Figure 1. Trial Design



D. DEFINITION OF TREATMENT SUCCESS AND FAILURE

Overall treatment success is defined as:

- a negative pad test (<15 ml urine leakage over 24 hours); and
- no self-reported leakage by 3-day voiding diary; and
- no self-reported stress-type UI symptoms (MESA questionnaire: response of "rarely" or "never" for each stress-type symptom); and
- a negative stress test; and
- no retreatment for SUI (including anti-incontinence surgery, tightening of sling, collagen injections, medication, behavioral treatment, etc.).

Although treatment success will be evaluated at several time points, the a priori primary time point for evaluating success is at 24-months.

Because the urge component of incontinence in women with mixed incontinence is not expected to be improved by either surgical procedure being studied, the requirement of negative self-report and negative pad test may prevent women from achieving the clinical endpoint of "success" even if the surgery is successful in eliminating the stress component of incontinence. Therefore, a second definition of treatment success specific to SUI consists of:

- a negative stress test; and
- no self-reported stress-type UI symptoms (response of "never" or "rarely" for each stress-type symptom on MESA questionnaire); and
- no retreatment for SUI (including anti-incontinence surgery, tightening of sling, collagen injections, medication, behavioral treatment, etc.).

Overall treatment failure is defined as:

- any surgical, pharmacological or behavioral retreatment for SUI at any point after the initial surgery for urine leakage; or
- any one of the following ≥6 months after surgery:
  1. a positive stress test, or
  2. self-reported stress-type UI symptoms (response of "sometimes" or "often" on the MESA questionnaire); or
  3. a positive pad test (≥15 ml leakage over 24 hours), or
  4. self-reported leakage by 3-day voiding diary.

Similarly, treatment failure specific to SUI is defined as:

- any surgical, pharmacological or behavioral retreatment for SUI at any point after the initial surgery for urine leakage; or
- any one of the following ≥6months after surgery:
  1. a positive stress test, or
  2. self-reported stress-type UI symptoms (response of "sometimes" or "often" on the MESA questionnaire)

Once a woman is documented as a treatment failure, she cannot be classified as a success for that endpoint at later time points.

E. STUDY POPULATION

The study population will consist of women who have been diagnosed with predominant stress urinary incontinence (SUI).

E.1 Inclusion Criteria

1. Female
2. Predominant SUI as evidenced by:
   - Self-reported stress-type UI symptoms, of duration ≥3 months*
   - Mean micturition <12x/day
   - MESA stress symptom score (percent of total possible stress score) greater than MESA urge symptom score (percent of total possible urge score)
   - Observation of leakage by provocative Stress Test at a bladder volume ≤300ml (Valsalva or cough-induced detrusor instability is considered mixed UI and therefore allowed.)
   - Maximum cystometric capacity ≥200ml
   - Post-void residual (PVR) ≤150cc by Stress Test or UDS with pelvic organ prolapse (POP) Stage I or lower. If POP is Stage II-IV, PVR >150cc is allowed.
   - Voiding not obstructed: maximum flow rate ≥12ml/sec, PVR ≤150cc, and detrusor pressure at maximum flow ≤50cm H_2O. If POP Stage II-IV, maximum flow rate <12 ml/sec, PVR >150cc, and/or detrusor pressure at maximum >50cm H_2O is allowed.
3. Urethral hypermobility as evidenced by resting angle >30° or maximum straining angle >30° on Q-Tip Test
4. Eligible for both Burch and sling procedures
   - No medical contraindications, e.g., current UTI, history of pelvic irradiation, history of lower urinary tract cancer
   - ASA class I, II, or III
   - No current intermittent catheterization
   - Candidate for harvesting of autologous rectus fascia graft
5. Available for 24-months of follow-up and able to complete study assessments, per clinician judgment.
6. Signed consent form

*Patient can be deferred for enrollment until respective time interval has been met.

E.2 Exclusion Criteria

1. Age <21 years
2. Non-ambulatory (Ambulatory with assistive devices does not exclude the patient.)
3. Pregnancy by self-report or positive pregnancy test, or self-reported intention to become pregnant in the next 24-months
4. Current cancer chemotherapy or radiation therapy
5. Systemic disease known to affect bladder function (i.e., Parkinson's disease, multiple sclerosis, spina bifida, spinal cord injury or trauma)
6. Urethral diverticulum, current or previous (i.e. repaired)
7. Prior augmentation cystoplasty or artificial sphincter
8. <12 months post-partum*†

9. Recent pelvic surgery (e.g. vaginal hysterectomy), i.e., endoscopic pelvic surgery <6 weeks or open pelvic surgery <6 months*
10. Participation in another treatment intervention trial that might influence the results of this trial.

*Patient can be deferred for enrollment until respective time interval has been met.

†"Partum" is defined as a delivery or other termination that occurs after 20 weeks.

If more than 6-months transpires between determination of eligibility and surgery, specified measures must be repeated to ensure current eligibility for the trial as well as to obtain current baseline values for critical measures that are subject to change. (See Section H.5 and Appendix A.)

F. RANDOMIZATION

Patients will be randomized in the operating room. It is recognized that there are disadvantages to this strategy, including the following points:

- Patients must agree to be blinded to the type of surgery they will get until after the operation;
- The surgeon(s) must be prepared to perform either type of procedure;
- The anesthesiologist must be willing and able to evaluate the patient without knowing which procedure will be performed.

The process of obtaining the randomized treatment assignment will be accomplished via a telephone call to an automated randomization system at the Biostatistical Coordinating Center (New England Research Institutes) from a touchtone telephone. A back-up hard copy of the assignment kept in a sealed envelope will be made available in the case of technical problems. Randomization will be stratified by clinical site, using permuted blocks.

G. TREATMENTS

G.1 Operative Procedures

The two procedures included in this trial are the Burch modified Tanagho procedure and the autologous fascia sling procedure.

G.2 Standardization of Operative Procedures

Recognizing the need for both internal and external validity, the two procedures will be standardized across participating surgeons as follows:

a. Sling

- Sling material: autologous rectus fascia
- Size: at least 2x6cm
- Suture material: polypropylene; gauge $\geq$0
- Site of sling placement: proximal half of urethra, bladder neck to mid-urethra
- NO visible evidence of angulation of the urethra/bladder neck at end of procedure and NO tension on the sling
- Cystoscopy to confirm no stitches in the bladder and ureteral function
- Mechanical drainage: suprapubic or Foley catheter

- **b. Burch**
  - Incision: smallest possible (4-6cm unless BMI>30)
  - Number of sutures: 2-3 sutures on each side from anterior vagina to the ipsilateral Cooper's ligament
  - One set of sutures at urethrovesical junction
  - Suture material: polypropylene; gauge ≥0
  - Cystoscopy to confirm no sutures in the bladder and ureteral function
  - Sutures tied to elevate the anterior vagina to a minimally retropubic position
  - Mechanical drainage: suprapubic or Foley catheter

G.3 Allowable Modifications

Concurrent operations such as enterocele repair, colpopexy, cystocele and rectocele repair, hernia repair, hysterectomy, appendectomy, partial sigmoid colectomy, or others will be allowed. Concomitant surgeries will be monitored by the Executive Committee.

G.4 Modifications NOT Allowed

- Laparoscopic Burch or sling
- Transvaginal Burch
- TVT
- Sling material: synthetic material, dermis, small intestine submucosa [SIS], cadaveric tissue
- Bone anchors

G.5 Standardization of Material and Harvest Location for the Pubovaginal Sling

Material for the pubovaginal sling will be limited to autologous tissue. Further, the harvest location for this tissue will be limited to rectus fascia.

Both autologous and cadaveric sling material are considered current practice among all of the participating centers. Synthetic slings have had unacceptably high complication rates and have been largely replaced by fascial slings (Bent, Ostergard, & Zwick-Zaffuto, 1993; Leach et al., 1999) from these two sources. Most of the long-term data on slings comes from procedures performed with autologous grafts. In fact, there are no published trials comparing autologous and cadaveric materials.

The use of cadaveric fascia for pubovaginal slings has become increasingly popular, because this material may decrease operating time and patient discomfort, but also because of the increased availability of tissue banking. Autologous fascial slings involve an incision in the abdominal skin and fascia (rectus fascia) or in the thigh (fascia lata). Although these incisions are associated with little pain or discomfort for most patients, autologous grafts present a greater potential for pain than do cadaveric grafts. However, autologous grafts avoid the theoretical risk of infection, and offer a standardized source of tissue available at the time of randomization in the OR. While cadaveric fascia lata grafts offer some advantage in smaller skin incisions and no fascial incisions, there is a lack of standardization in cadaveric tissue sources and availability: fresh frozen or freeze-dried, age of donor, and techniques to sterilize the tissue. Further, the

question of graft autolysis associated with cadaveric slings (Fitzgerald, Mollenhauer, & Brubaker, 1999) raises concerns of safety.

Without comparative data on the efficacy and particularly the durability of autologous and cadaveric sling tissue, there is the risk that variability in the sling material might dilute the efficacy and durability outcomes for the sling procedure compared to the Burch. Therefore, to eliminate this potential source of variability, the sling material will be limited to autologous tissue for this trial. To further limit variability and the number of incisions (i.e. to one, suprapubic), the harvest location is limited to rectus fascia.

G.6 Standardization of Post-Op Catheter Removal

Following surgery, a patient might be discharged having resumed spontaneous voiding or requiring one of the following three means of bladder drainage. Removal or discontinuation of the catheter is standardized as follows:

1. Continuous Foley Drainage
   - Patient discharged home with indwelling Foley catheter.
   - Remove Foley by at least POD #5: after bladder filled retrograde to 300cc.
     - If patient able to void at least 150cc, Foley not reinserted;
     - If patient voids less than 150cc, Foley may be reinserted; or
     - Patient can be taught CISC.
   - Check voiding capabilities q 3-5 days as above until PVR <150cc.
2. Suprapubic Catheter
   - Catheter to be removed once both morning and evening residuals are below 150cc.
3. Clean Intermittent Self Catheterization (CISC)
   - Catheterization to be discontinued once both morning and evening residuals are below 150 cc.

G.7 Post-Op Treatment of Complications

The following post-operative treatment will be allowed:

- For retention: no surgical treatment until ≥6 weeks post-op.
- For urgency, frequency, nocturia >2x/night: at MD discretion.
- If pre-operative treatment for urge incontinence: resume at MD discretion.

G.8 Post-Operative Instructions

Post-operative instructions for patients are at the discretion of the treating surgeon/facility. A set of instructions to serve as a guideline are included in Appendix D.

H. MEASUREMENT

H.1 Primary Outcome Measures

a. Voiding Diary

Self-monitoring of voiding behavior and frequency using a daily dairy is a practical and reliable method for assessing the frequency of voluntary micturitions and involuntary episodes of urine loss (Locher, Goode, Roth, Worrell, & Burgio, 2001; Nygaard & Holcomb, 2000; Wyman, Choi, Harkins, Wilson, & Fantl, 1988). The diary has the advantages of reducing recall error and results in higher levels of reporting for most conditions (Verbugge, 1980). Several variations of a urinary diary have been used for clinical and research purposes. Recommended duration for

keeping the diary ranges from 3 –14 days (Burton, 1984; Robb, 1985). For purposes of this trial, a 3-day diary will be used, based on the results of reliability testing by Nygaard and Holcomb (2000) in women with genuine SUI. They reported a correlation of 0.887 between the first 3 days of a diary and the last 4 days, suggesting that a 3-day diary is an appropriate outcome measure for clinical trials evaluating treatments for SUI.

b. Pad Test

Pad testing is used as a means of quantifying the amount of urine involuntarily lost. The 24-hour pad test will be used to reflect everyday incontinence (Jorgensen, Lose, & Thunedborg, 1987). The test has been standardized by the International Continence Society (ICS) (Abrams, Baivas, Stanton, & Anderson, 1988), correlates well with UI symptoms (Lose & Versi, 1992), and has good reproducibility (Jorgensen, Steen, Bagger, & Fisher-Rasmussen, 1985).

c. Self-Reported Stress-Type UI Symptoms

Self-reported stress-type UI symptoms will be collected using selected items regarding stress and urge-type UI symptoms taken from the questionnaire for the Medical, Epidemiologic, and Social Aspects of Aging Project (MESA) conducted at the University of Michigan (Herzog, Diokno, Brown, Normolle, & Brock, 1990). The items query the patient's description of how urine loss occurred. Questions referring to loss of urine at times of exertion such as laughing, sneezing, lifting, or bending over define SUI. Questions referring to urine loss preceded by an urge to void, or uncontrollable voiding with little or no warning define urge incontinence. Symptoms associated with urine loss of both urge and stress-types define "mixed" incontinence. For the purposes of this trial, predominant SUI is defined as the percent of stress-type symptoms > the percent of urge-type symptoms. Agreement between the MESA questions and a clinician's assessment has been reported as 87% for women (Herzog et al., 1990). The authors further noted that self-reported stress-type symptoms had an accuracy of 69% in predicting a urodynamic diagnosis of SUI.

d. Stress Test

A provocative stress test will be performed for direct observation of urine leakage (Shull et al., 1999). Observed urine loss from the urethra coincidental with the Valsalva maneuver or cough is a positive test.

e. Need for Retreatment or Additional Surgery

The need for any additional treatment for SUI at any time after the index procedure will constitute a treatment failure. Additional treatment includes additional anti-incontinence surgery, tightening of the sling, collagen injections, and medications or behavioral treatments specific to SUI as follows:

Surgery:

- Burch colposuspension
- Sling procedure (including tightening of previous sling procedure)
- Needle suspension (Raz, Pereyra, Stamey, Gittes, etc.)
- Suburethral plication
- Collagen injection

  (NB: Surgery for prolapse is not defined as failure of SUI procedure.)

  (NB: Surgical "take down" of a sling is not defined as failure of SUI procedure; rather, "take down" is considered a complication, as is the broader category of voiding dysfunctions requiring treatment.)

NOTE: UDS must be conducted <u>prior</u> to any surgery for voiding dysfunction.

Pharmacologic treatment:

- Alpha-agonists
  (NB: Estrogen treatment is not defined as failure of SUI procedure.)

Other treatments:

- Pelvic muscle rehabilitation (with or without biofeedback) for the indication of treatment of SUI
  (NB: PMR for treatment of urge incontinence is not defined as failure of SUI procedure.)
- Devices such as vaginal cones, pessary, urethral plugs or patches for SUI
  (NB: Pessary for prolapse is not defined as failure of SUI procedure.)

H.2 Secondary Outcome Measures

a. Quality of Life

Because no direct relationship has been reported between a patient's level of distress and a patient's level of satisfaction with treatment, it will be important to measure the impact of treatment outcome on the patient's quality of life (QOL). Health-related QOL is a multidimensional concept which encompasses well-being that is related to health and is distinguished from measures of health and functional status. A condition-specific measure will be used in this trial so as to be sensitive enough to detect change, i.e. the Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory (UDI) developed by Shumaker et al (1994). The former measure assesses the impact of UI on various activities, roles, and emotional states, whereas the latter measure assesses the degree to which UI symptoms are troubling to women. Adequate validity, reliability and sensitivity to change have been reported by the authors.

b. Sexual Function

Little is known about the sexual functioning of women with UI. As with measurement of QOL, a condition-specific measure of sexual function will be used in this trial. The short form of the Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) developed by Rogers et al (2001) is a 12-item self-administered questionnaire. Adequate validity, reliability, and sensitivity to change have been reported by the authors (Rogers, Qualls, Kammerer-Doak, & Coates, 2001 b). A Spanish version of the PISQ-12 has been validated (Rogers, personal communication, 8/31/01) and is available for use in this trial.

c. Satisfaction with Treatment Outcome

Due to the increasing concern regarding patient satisfaction with medical care and the documented association between satisfaction and treatment adherence (Lochman, 1983), patient satisfaction has been included as a secondary outcome. A 9-item self-administered questionnaire has been developed to assess this outcome. These items measure patient satisfaction with the result of surgery related to activities previously restricted by UI symptoms and to emotions associated with UI, as well as providing a measure of patients' global sense of satisfaction with the outcome. Because it has been established that treatment satisfaction is affected by the patient's pre-treatment expectations of the outcome (Mancuso, Salvati, Johanson, Peterson, & Charlson, 1997; Williams, Weinman, Dale, & Newman, 1995; Wilson, Saling, Kincade, & Bladin, 1998), an accompanying measure of treatment expectations has also been developed. The 10-item self-administered questionnaire measures expectations of improvement in UI symptoms, improvement in activities limited by UI, and improvement in emotions associated

with UI. Both of these measures are currently being tested for validity and reliability at the University of Pittsburgh.

H.3 Independent Variables

There are four groups of independent variables:

- *Sociodemographic characteristics*: age; race; marital status; education; occupation; annual income; insurance status
- *Risk factors for UI*: age (Milsom, Ekelund, Molander, Arvidsson, & Areskoug, 1993; Yarnell, Voyle, Richards, & Stephenson, 1981); parity (Burgio, Locher, Zyczynski, Hardin, & Singh, 1996; Foldspang, Mommsen, Lam, & Elving, 1992; Jolleys, 1988; Sommer et al., 1990; Thomas, Plymat, Blannin, & Meade, 1980; Yarnell, Voyle, Richards, & Stephenson, 1982); weight of largest baby; menopause status and use of HRT (Burgio et al., 1991; Jolleys, 1988); BMI (Brown et al., 1996; Burgio et al., 1991; Mommsen & Foldspang, 1994; Yarnell et al., 1982); previous anti-incontinence and gynecologic surgery (Jolleys, 1988; Milsom et al., 1993); current medications (Montella & Wordell, 1996)
- *Type and severity of UI* measured by the following: MESA questionnaire (Herzog et al., 1990); stress test; Q-Tip Test; Pad Test; Voiding Diary; Urodynamic Studies (i.e.,uroflowmetry; cystometrogram; pressure flow study)
- *Urodynamic Studies*, including uroflowmetry; cystometrogram; pressure flow studies

H.4 Intervening Variables

Intervening variables that might affect the outcomes of interest consist of the following four categories:

- *Pelvic comorbidity*: pelvic organ prolapse (POP-Q quantification)
- *Intraoperative considerations*: surgical and medical complications (see Appendix B); length of procedure; estimated blood loss (see Appendix C)
- *Postoperative considerations*: length of hospital stay; post-operative pain; medical complications (e.g., pulmonary, febrile morbidity, cardiovascular, neurologic, urinary tract; see Appendix B); de novo or recurrent urinary urgency or urge incontinence; other non-surgical treatments
- *Patient expectations of surgery*

H.5 Schedule of Measurements

The schedule of measurements is included in Appendix A. Data will be collected during clinic visits at baseline, 6-weeks, 6-months, 12-months, and 24-months, and by mail or telephone at 3-months and 18-months.

For those patients determined to be a treatment failure because of surgical retreatment for SUI, the 24-month assessment battery will be completed at the time that this surgical retreatment is determined necessary (i.e. before the surgical retreatment). Follow-up visits will continue as scheduled with one exception to the assessment battery at 24 months, i.e. UDS will not be required at 24-months as testing was conducted prior to surgical retreatment. For those patients determined to be a treatment failure for all other reasons, the 24-month assessment battery will be completed at the time that this treatment is determined necessary, but further follow-up assessments will continue as scheduled. If the

out-of-sequence 24-month assessment is performed within the specified window for the next assessment, then that next assessment can be omitted.

If more than 6 months transpires between determination of eligibility and surgery, the following measures must be repeated to ensure current eligibility for the trial as well as to obtain current baseline values for critical measures that would be subject to change over a 6-month period.

1) The MESA assessment (Data Form 01, Sections C and D),
2) Recent pelvic surgery (Data Form 02, Section C),
3) Medication Audit (Data Form 03),
4) POP-Q examination (Data Form 04, Section E),
5) The Pad Test (Data Form 06, Section B),
6) The Voiding Diary (Data Form 06, Section C),
7) Expectations of Surgery (Data Form 07, Section B),
8) Quality of Life (Data Form 07, Section C),
9) Normal Activities (Data Form 07, Section D),
10) Sexual Function (Data Form 07 Section E), and,
11) All other eligibility criteria that might be subject to change over a 6-month period including:
    - Current UTI,
    - Pregnancy status (Data Form 01, Section E & Form 04 Section H),
    - Recent diagnosis of lower urinary tract cancer, Parkinson's Disease, multiple sclerosis, spinal cord injury or trauma (Data Form 02, Section B),
    - Report or evidence of urethral diverticulum, prior augmentation cystoplasty or artificial sphincter (Data Form 02, Section B, & Form 04, Section H),
    - Current intermittent catheterization (Data Form 02, Section B),
    - Current cancer chemotherapy or radiation therapy (Data Form 02, Section B),
    - ASA classification (Data Form 04, Section H),
    - Candidate for harvesting of autologous rectus fascia graft (Data Form 04, Section H).

The UDS, Q-Tip Test and the Stress Test do <u>not</u> have to be repeated.

I. TESTING PROCEDURES

I.1 Physical Exam and History

The following data will be collected from the pre-operative history and physical examination.

a. History:

- age
- race
- pregnancies (parity, weight of largest baby, number of vaginal deliveries)
- past pelvic surgeries
- history of estrogen replacement therapy
- duration of incontinence
- smoking history
- occupational history
- past surgical and medical incontinence treatments

- frequent UTIs, defined as >3 in previous 12 months
- bowel function, including fecal incontinence

b. Examination:

- height and weight (for BMI)
- directed neurological exam: to be recorded as present/absent OR normal/decreased:
    - deep tendon reflex knee
    - perineal sensation
    - anal sphincter voluntary contractions
- strength of pubococcygeus muscle (9-point scale based on strength, duration and movement observed with muscle contraction; (Brink, Well, Sampselle, Tailllie, & Mayer, 1994)

c. Q-Tip Test

The Q-Tip Test (Crystie, Charme, & Copeland, 1971) will be used to quantify bladder neck mobility using a standardized procedure as described in the Physical Examination Procedures Manual.

d. Pelvic Organ Prolapse Quantification (POP-Q)

The pelvic organ prolapse evaluation will be performed according to the guidelines established by the International Continence Society (Bump et al., 1996). The procedure will be standardized as demonstrated in a videotape produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Examination") and described in the Physical Examination Procedures Manual.

e. Provocative Stress Test

A standardized provocative stress test procedure will be performed for eligibility determination as described in the Stress Test Procedures Manual.

I.2 Pad Test

The Pad Test will be 24-hours in duration. All sites will use the same materials (pads and biohazard plastic zip-lock bags) and the same brand/model of scale for weighing the pads. All pads will be weighed individually in their biohazard bags.

The Pad Test will be done over a 24-hour period during the three voiding diary days. The only data to be collected will be the number and weight of pads worn by the patient. Pad Test instructions for patients will be provided on a videotape produced for this purpose.

I.3 Urodynamic Studies (UDS)

The order and procedures for urodynamic testing and the required measures of standardization are covered in detail in the UDS Procedures Manual in the Manual of Operations. UDS will be conducted at baseline and at 24-months post-surgery. The treating MD might decide to conduct UDS earlier than 24-months if a patient complains of, or has evidence of, voiding difficulties/dysfunction. However, follow-up UDS will be conducted no earlier than 4-weeks post-operatively as any voiding dysfunction during that time would fall under the definition of temporary.

Two additional timepoints at which UDS is required are as follows: 1) If a patient is going to have surgery post-UITN surgery for voiding dysfunction, it is <u>required</u> that the Investigator conduct UDS on the patient prior to that surgery; 2) If a patient is deemed a "treatment failure" prior to 24 months post-op, UDS will be conducted (along with the entire 24 month battery) at that time.

J. ADVERSE EVENT REPORTING AND THE DSMB

Adverse events (AEs) will be reported in accordance with the Department of Health and Human Services (DHHS) code of federal regulations (Title 45, Part 46). (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm). As required, a Data and Safety Monitoring Board (DSMB) has been organized. The DSMB is scheduled to meet every 6 months, once by teleconference and once in-person in a 12-month period.

Adverse events, defined as "unanticipated problems," have been specified for this trial. The list of reportable AEs was approved by the DSMB and is provided in Appendix B and at the bottom of the Adverse Event Form. There are two categories of AEs: 1) Serious Adverse Events and 2) Adverse Events. Serious adverse events are required to be reported to the BCC and NIDDK within 72 hours of occurrence or knowledge of the event. Adverse events not in the "serious" category, but judged to be "severe" or "life threatening" are also subject to the 72 hour reporting requirement. This reporting requirement is met by completing an Adverse Event Form and faxing it to the BCC and NIDDK. Copies of reports of all SAEs will be forwarded to the Chairperson of the DSMB.

At the bi-annual meetings of the DSMB, summary reports of all reportable AEs will be reviewed. The BCC is responsible for preparing these summary reports. Interim monitoring by the DSMB is also discussed in Section K2. After review, the Executive Secretary of the UITN DSMB is responsible for generating a brief summary report for distribution to all clinical sites, the BCC, and NIDDK. The report will document that a review of data and outcomes across all centers took place on a given date. It will also inform Investigators of the DSMB's conclusion with respect to progress or need for modification of the protocol. Investigators are required to submit a copy of this report to their local IRB. If there is any correspondence with the DSMB outside of the planned meetings that has study-wide implications, it is the responsibility of the Executive Secretary of the UITN DSMB to draft an appropriate memo for distribution to all clinical sites, the BCC, and NIDDK. Again, Investigators are responsible for submitting a copy of this correspondence to their IRB.

K. STATISTICAL CONSIDERATIONS

K.1 Sample Size Determination for Primary Endpoints

Two primary endpoints will be used: 1) "overall treatment success" to evaluate a broadly defined pragmatic benefit of surgery and 2) "treatment success specific to SUI" to evaluate a more narrow and mechanistic measure of benefit. See Section D for criteria. The primary time point for evaluating success is at 24-months. Although these measures of success cannot be fully documented until 24-months, a failure can be documented earlier (if, for example, a patient requires surgical treatment or has a positive stress test at 12-months).

Because the urge component of incontinence in women with mixed incontinence is not expected to be improved by either surgical procedure being studied, the requirement of negative self-report and negative pad test may prevent women from achieving the clinical endpoint of "overall treatment success" even if the surgery is successful in eliminating the stress component of incontinence. Therefore, although many reports of both Burch and sling procedures suggest "success" rates of approximately 80-85%, we expect to observe lower success rates in this trial, by approximately 15-20 percentage points. A sample size of 260 per group, or 520 total, would

ensure 80% power to detect a 12 percentage point difference (60% vs. 72%) using a two-sided α=.05 Fisher's exact test. In order to meet the criteria for success, patients must be willing to undergo a fairly intensive measurement process (self-administered questionnaire, 3-day diary, 24-hour pad test, stress test). It seems likely that some women who consider themselves to be cured will not comply with this regimen. Therefore, to adjust for a 20% non-compliance rate, the target sample size will be inflated to 325 per group, or 650 total.

For the more mechanistic endpoint, "treatment success specific to SUI," we assume a higher success rate, i.e., >80%. The target sample size will ensure >85% power for detecting a 10 percentage point difference (80% vs. 90%).

K.2 Interim Monitoring

Ordinarily, early stopping rules are based on monitoring the primary endpoints for a treatment difference so large that it is unethical to continue treating one group of patients with the "inferior" treatment, and on monitoring the treatments for safety. In this trial, however, several considerations argue against the usual motivations for early stopping procedures.

First, we expect very little primary endpoint data to be available while any participants are still at risk for exposure to either surgery being evaluated. Accrual is expected to take 24-months and success on the primary endpoints is not documented until 24-months after surgery. Therefore, at the time the first participants are reaching the assessment time for documenting "success", all or nearly all patients will already have had their surgery. Nevertheless, there will be some information on the primary endpoints prior to 24-months, since self-reported stress-type symptoms, a positive diary, positive pad test or positive stress test at 6-24 months, or retreatment for SUI at any time prior to 24-months will be considered a failure.

Second, both the Burch modified Tanagho and the autologous fascia sling procedures are "standard" surgical procedures. Unlike a trial evaluating a new surgical procedure, the study procedures in this trial have generally well-known complications. It is unlikely that we will experience any new or unexpected complications. Of course, we will collect and document complications but we do not expect that treatment group differences in surgical complication rates would pose an ethical imperative to stop the trial, unless some serious unexpected complication is prevalent. Rates of the more serious surgical complications (e.g. organ damage, sling erosion, hernia, wound infection) will be summarized separately within each site and further within each surgeon, to monitor for problems with specific hospitals or surgeons.

Formal interim data monitoring will be based on a time-to-event analysis, specifically a logrank test, with the event defined as failure of the primary endpoint, as defined in Section D. With an anticipated 60-72% success rate, we expect about 35% of patients to "fail", or about 200 failures. Formal interim hypothesis testing will be performed after approximately 50, 100, and 150 failures have occurred. The methodology of Lan and DeMets will be used to implement an O'Brien-Fleming stopping boundary for this monitoring. The Lan and DeMets methodology allows flexibility in the exact timing of the interim analyses, so that for example a DSMB meeting can be scheduled for when approximately 50 failures are expected to have occurred, but if the actual count is not exactly 50, the stopping boundary can be adjusted accordingly. The O'Brien-Fleming boundary is probably the most commonly used stopping boundary because it is conservative early in the trial (i.e. a very strong treatment difference is required for stopping) but maintains close to the nominal significance level toward the end of the trial (i.e. almost any p-value less than .05 at the end of the trial can be considered "significant").

In addition, treatment differences for any endpoint significant at the .001 level will be brought to the attention of the DSMB for consideration of possible early stopping.

Any early stopping boundary should be considered a guideline and not a hard-and-fast rule. Instead, the evidence should be considered in the context of other study data. Accordingly, DSMB reports will ordinarily include summaries of a variety of endpoints, patient characteristics, adverse events, data quality, and any unanticipated problems that arise during the conduct of the trial.

K.3 Analytic Approach

Fisher's exact test will be used for unadjusted analysis of the primary endpoints and other dichotomous outcomes (e.g. complication rates). Time-to-failure analyses (Kaplan-Meier plots and logrank tests) will also be used in secondary analyses of the primary outcome as described above under "Interim Monitoring." Treatment comparisons will be adjusted for covariates with the logistic model for dichotomous endpoints and proportional hazards models for time-to-failure analyses. Analysis of continuous outcomes such as the quality of life subscales will be based on change from baseline. Prognostic models will be developed using baseline urodynamic testing results and other baseline covariates to explore the extent to which baseline measures can be used to predict surgical success. Time-to-event methods will be utilized to characterize time to normal voiding. In addition to comparing treatment groups with respect to satisfaction with surgery, the analysis of this outcome will include an evaluation of expectations of surgery as a predictor of satisfaction.

L. RECRUITMENT

To assess ability of the nine clinical centers to enroll the required number of patients (73 patients per center) into the trial over a two-year period, each center provided data in July 2001 regarding the number of Burch and sling procedures performed over the prior 12-months. These data are displayed in Table 2. Based on these data and the estimated enrollment rate of 20% of eligible patients, there appear to be a sufficient pool of patients from which to recruit. In the event that the enrollment rate has been overestimated (i.e. fewer patients agree to participate in the trial), several additional sources of potential patients have been identified:

- Investigator's office (might include patients of a non-study surgeon in a group practice);
- Referrals from colleagues;
- Post-card announcements in clinical areas/offices;
- Advertising: newspapers; newsletters; cable TV or public service announcements; websites of professional organizations, advocacy groups, or NIH; health fairs, health clubs, billboards;
- Mailings to enriched lists, e.g., former patients.

Table 2. Number of Procedures by Site: Approximate 12 Months prior to July 2001

Site	Burch	Sling
University of Alabama - Birmingham	68	162
University of California - San Diego	123	152
University of Maryland	46	155
University of Pittsburgh	33	297
University of Texas - Dallas	141	102
University of Texas - San Antonio	5	93
University of Utah	636	65
Beaumont Hospital	89	163
Loyola University	*	*
Total	**1141**	**1189**

*Not a participating center at time of survey

M. INFORMED CONSENT PROCEDURES

It is expected that patients will undergo clinical assessment for type of urinary incontinence and candidacy for surgery. If a patient appears to be eligible for the study, including eligibility for either a Burch or sling procedure, she will be approached about the study. The patient will be asked to view a videotaped description of the trial (presented by the Steering Committee Chair, Dr. William Steers) and then will be presented with the informed consent form by study personnel, either the surgeon or research nurse. Written informed consent will be obtained prior to proceeding with any further eligibility determination, testing, or data collection activities.

Templates for the informed consent forms 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.

N. DATA MANAGEMENT

A customized data management system (DMS) has been developed for this study using the Biostatistical Coordinating Center's Web-based Advanced Data Entry and Protocol Tracking (ADEPT) system. ADEPT integrates all aspects of study data collection including: participant screening and enrollment data; real time accrual reporting; tracking of participant study appointments for follow-up; all study follow-up data collection; censoring/loss to follow-up data; and monitoring timeliness and quality of data collection. Data are stored in an Oracle relational database at the BCC. CTCs enter data via a customized ADEPT secure web application that provides real-time field level validations and context sensitive help. HTML data entry forms are enhanced with client side JavaScript code to ensure rapid entry of study forms, proper validations of all data fields and proper skip patterns within study data forms. Interim background data submittals prevent loss of data due to loss of internet connections.

N.1 Data Entry

ADEPT includes a number of standard features designed to ensure consistently high quality data. Integrated into the data entry system are real time validations, including both inter- and intra-instrument data checks. Inconsistent or questionable values are flagged during entry, and an edit report is automatically generated. These edit reports are designed to be human readable, listing the participant ID, the instrument name, and a detailed description of why each

specific data item was flagged. The edit report can be printed out and reviewed by a supervisor or returned to the data collector for resolution. The ADEPT system also tracks missing data rates by instrument and data collector. Data entry quality is monitored through a sample-based double data entry system. A self-adjusting algorithm is used to enforce a higher double data entry rate on keyers who have higher error rates.

N.2 Data Security and Integrity

The web based components of the data management system utilize several levels of security to ensure privacy and integrity of the study data:

- Web Access requires use of assigned user names and passwords.
- Passwords will be changed every 90 days.
- Web based entry uses secure socket layer data encryption.
- Firewall protects against unauthorized access to study data.

All study data will be stored on the BCC's NT based Oracle server. Access to data on this server (from both inside and outside the data center) is controlled by Oracle's extensive security features. Oracle archiving and backup system ensures minimal data loss even in the most catastrophic system failure. Backup data tapes are stored off site in a nearby bank safety deposit box.

O. QUALITY CONTROL ACTIVITIES

The BCC has primary responsibility for QC/QA activities. The BCC also requires that the sites complete certain QC activities, most of which are monitored by the BCC.

The key QC/QA activities are:

- Development of a study Manual of Operations as well Procedures Manuals (for surgical procedures, urodynamic studies, other physical tests)
- Clearly formatted and carefully constructed Data Forms, clearly linked to the research questions and research models, with clear, up-to-date manuals of instruction;
- Sign-Off Procedures for all study forms;
- Central training, with hands-on practice and certification, of all CTC data collection staff with the use of standardized checklists;
- Certification of all participating surgeons in the surgical procedures;
- Certification of all participating clinicians in performance of urodynamic studies and staging of pelvic organ prolapse;
- Central training and certification of CTC data managers;
- Verification of patient eligibility;
- On-going monitoring of all protocols/data collection activities;
- Completion of reliability and/or pilot studies for *key measurements* as appropriate;
- Use of standard (or standardized) equipment that is calibrated on a regular schedule;
- Inclusion of repeat measurements, as feasible, in the course of the study; and
- At least annual site visits to all CTCs with pre-specified goals.

REFERENCES

Abrams, P., Blaivas, J. G., Stanton, S. L., & Anderson, J. T. (1988). Standardisation of terminology of lower urinary tract function. The International Continence Society Committee in Standardisation of Terminology. Neurourology and Urodynamics, 7, 404.

Bent, A. E., Ostergard, D. R., & Zwick-Zaffuto, M. (1993). Tissue reaction to expanded polytetrafluoroethylene suburethral sling for urinary incontinence: clinical and histologic study. American Journal of Obstetrics and Gynecology, 169(5), 1198-1204.

Black, N. A., & Downs, S. H. (1996). The effectiveness of surgery for stress incontinence in women - a systematic review. British Journal of Urology, 78, 497-510.

Brink, C. A., Well, T. J., Sampselle, C. M., Tailllie, E. R., & Mayer, R. (1994). A digital test for pelvic muscle strength in women with urinary incontinence. Nursing Research, 43(6), 352-356.

Brown, J. S., Seeley, D. G., Fong, J., Black, D. M., Ensrud, K. E., & Grady, D. (1996). Urinary incontinence in older women: Who is at risk? Study of osteoporotic fractures research group. Obstetrics and Gynecology, 87(5 Pt 1), 715.

Bump, R. C., Mattiasson, A., Bo, K., Brubaker, L. P., Delancey, J. O. L., Shull, B. L., & Smith, A. R. B. (1996). The standardisation of terminology of female pelvic organ prolapse and pelvic floor dysfunction. American Journal of Obstetrics and Gynecology, 175, 10-17.

Burgio, K. L., Locher, J. L., Zyczynski, G., Hardin, J. M., & Singh, K. (1996). Urinary incontinence during pregnancy in a racially mixed sample: characteristics and predisposing factors. International Urogynecological Journal of Pelvic Floor Dysfunction, 7, 69.

Burgio, K. L., Matthewss, K. A., & Engel, B. T. (1991). Prevalence, incidence, and correlates of urinary incontinence in healthy, middle-aged women. Journal of Urology, 146, 1255.

Burton, J. R. (1984). Managing urinary incontinence - a common geriatric problem. Geriatrics, 39, 46-51.

Crystie, C. C., Charme, L. S., & Copeland, W. E. (1971). Q-tip test in stress urinary incontinence. Obstetrics and Gynecology, 38, 313-315.

Enzelsberger, H., Helmer, H., & Schatten, C. (1996). Comparison of Burch and Lyodura sling procedures for repair of unsuccessful incontinence surgery. Obstetrics and Gynecology, 88, 251-256.

Fantl, J. A., Newman, D. K., Colling, J., & al, e. (1996). Urinary incontinence in adults: Acute and chronic management. Clinical practice guideline, No 2, 1996. (AHCPR Publication No. 96-0682). Rockville, MD: U.S. Department of Health and Human Services. Publich Health Service, Agency for Health Care Policy and Research.

Fitzgerald, M. P., Mollenhauer, J., & Brubaker, L. (1999). Failure of allograft suburethral slings. BJU Int, 84(7), 785-788.

Foldspang, A., Mommsen, S., Lam, G. W., & Elving, L. (1992). Parity as a correlate of adult female urinary incontinence prevalence. Journal of Epidemiological Community Health, 46, 595.

Henriksson, L., & Ulmsten, U. (1978). A urodynamic evaluation of the effects of abdominal urethrocystopexy and vaginal sling urethroplasty in women with stress incontinence. American Journal Obstetrics and Gynecology, 131, 77-82.

Herzog, A. R., Diokno, A. C., Brown, M. B., Normolle, D. P., & Brock, B. M. (1990). Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. Journal of Gerontology: Medical Sciences, 45(2), M67-M74.

Hunskaar, S., & Vinsnes, A. (1991). The quality of life in women with urinary incontinence as measured by the sickness impact profile. JAGS, 39, 378-382.

Iosif, C. S. (1983). Results of various operations for urinary stress incontinence. Arch Gynecol, 233, 93-100.

Jarvis, G. J., Bent, A., Cortesse, E., McGuire, E., Milani, R., Quartey, J., Richard, F., Smith, A., Zimmern, P., & Ghoneim, J. (1999). Surgical treatment incontinence in adult women - Surgery of female lower genito-urinary fistuale. In P. Abrams, K. Saad, & A. Wein (Eds.), Incontinence: Proceedings of the 1st International Consultation on Incontinence - June 28-July 1, 1998 - Monaco . St. Helier, England: Health Publications Ltd.

Jolleys, J. V. (1988). Reported prevalence of urinary incontinence in women in a general practice. British Medical Journal, 296, 1300.

Jorgensen, L., Lose, G., & Thunedborg, P. (1987). Diagnosis of mild stress incontinence in females; 24-hour home pad weighing test versus the 1-hour ward test. Neurourological Urodynamics, 6, 165.

Jorgensen, L., Steen, A., Bagger, P. V., & Fisher-Rasmussen, W. (1985). The one-hour pad-weighing test for assessment of the result of female incontinence surgery. Paper presented at the Proceedings of the 15th Annual Meeting of the ICS, London.

Lalos, O., Burglund, A. L., & Bjerle, P. (1993). Urodynamics in women with stress incontinence before and after surgery. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 48, 197-205.

Leach, G. E., Dmochowski, R. R., Appell, R. A., Blaivas, J. J. G., Hadley, H. R., Luber, K. M., & al, e. (1997). Female stress urinary incontinence clinical guidelines: panel summary report on surgical management of female stress urinary incontinence. J Urol, 158, 875-880.

Leach, G. E., Kobashi, C. K., Mee, S. L., Zimmern, P., Nitti, V., & Mostwin, J. (1999). Erosion of woven polyester synthetic ("Protogen") pubovaginal sling. J Urol, 161, 106S.

Locher, J. L., Goode, P. S., Roth, D. L., Worrell, R. L., & Burgio, K. L. (2001). Reliability assessment of the bladder diary for urinary incontinence in older women. Journal of Gerontology: Medical Sciences, 56A(1), M32-M35.

Lochman, J. E. (1983). Factors related to patients' satisfaction with their medical care. Journal of Community Health, 9, 91.

Lose, G., & Versi, E. (1992). Pad-weighing tests in the diagnosis and quantification of incontinence. International Urogynecology, 3, 324.

Mancuso, C. A., Salvati, A., Johanson, N. A., Peterson, M. G. E., & Charlson, M. E. (1997). Patients expectations and satisfaction with total hip anthroplasty. Journal of Anthroplasty, 12, 387-396.

Marinkovic, S., Mian, H., Evanlovich, M., Poplawsky, D., Novi, J., Frey, C., & Yap, W. (1998). Analysis of early outcome: Burch procedure versus pubovaginal sling. Int.Urogynecol J and Pelvic Floor Dysfunc, 9, 94-99.

Milsom, I., Ekelund, P., Molander, U., Arvidsson, L., & Areskoug, B. (1993). The influence of age, parity, oral contraception, hysterectomy, and menopause on the prevalence of urinary incontinence in women. Journal of Urology, 149, 1459.

Mommsen, S., & Foldspang, A. (1994). Body mass index and adult female urinary incontinence. World Journal of Urology, 12, 319.

Montella, A. J., & Wordell, C. J. (1996). The effects of drugs on the lower urinary tract. In D. Ostergard & A. Bent (Eds.), Urogynecology and urodynamics . Baltimore: Williams and Wilkins.

Norton, P., MacDonald, L., Stanton, S., & Sedgwick, D. (1988). Distress and delay associated with female urinary complaints. Br Med J, 297, 1187-1189.

Nygaard, I., & Holcomb, R. (2000). Reproducibility of the seven-day voiding diary in women with stress urinary incontinence. International Urogynecology Journal, 11, 15-17.

Olsen, A., Smith, V., & Bergstrom, J. (1997). Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol, 89, 501-505.

Ostergard, D. R. (1997). Primary slings for everyone with genuine stress incontinence? The argument against. International Urogynecological Journal of Pelvic Floor Dysfunction, 8(6), 321-322.

Richmond, D. H., & Sutherst, J. R. (1989). Burch colposuspension or sling for stress incontinence? British Journal of Urology, 64, 600-603.

Robb, S. S. (1985). Urinary incontinence verification in elderly men. Nursing Research, 34, 278-282.

Rogers, R., Qualls, C., Kammerer-Doak, D., & Coates, K. (2001 b). Short form to assess sexual function in women with urinary incontinence and/or pelvic organ prolapse: the PSQ-11. International Urogynecology Journal and Pelvic Floor Dysfunction, 12(Suupl 1), S2.

Rogers, R. G., Kammerer-Doak, D., Villareal, A., Coates, K., & Qualls, C. (2001). A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. American Journal of Obstetrics and Gynecology, 184(4), 552-558.

Shull, B. L., Halaska, M., Hurt, G., Kinn, A., Laycock, J., Palmtag, H., Reilly, N., Yong Yang, & Zubieta, R. (1999). Physical examination. In P. Abrams, K. Saad, & A. Wein (Eds.), Incontinence: Proceedings of the 1st International Consultation on Incontinence - June 28-July 1, 1998 - Monaco . St. Helier, England: Health Publications Ltd.

Shumaker, S. A., Wyman, J. F., Uebersax, J. S., McClish, D., & Fantl, J. A. (1994). Health-related quality of life measures for women with urinary incontinence: The incontinence impact questionnaire and the urogential distress inventory. Quality of Life Research, 3, 291-306.

Sommer, P., Bauer, T., Nielsen, K. K., Kristensen, E. S., Hermann, G. G., Steven, K., & al, e. (1990). Voiding patterns of female urinary incontinence in women. A questionnaire survey. British Journal of Urology, 66, 12.

Thomas, T. M., Plymat, K. R., Blannin, J., & Meade, T. W. (1980). Prevalence of urinary incontinence. British Journal of Medicine, 281, 1243.

Verbugge, L. (1980). Health diaries. Medical Care, 18, 73-95.

Wagner, T. H., & Hu, T. W. (1998). Economic costs of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct, 9(3), 127-128.

Weber, A. M., & Walters, M. D. (2000). Burch procedure compared with sling for stress urinary incontinence: a decision analysis. Obstetrics and Gynecology, 96(6), 867-873.

Williams, S., Weinman, J., Dale, J., & Newman, S. (1995). Patient expectations: What do primary care patients want from the GP and how far does meeting expectations affect patient satisfaction? Family Practice, 12, 193-200.

Wilson, S. J., Saling, M. M., Kincade, P., & Bladin, P. F. (1998). Patient expectations of temporal lobe surgery. Epilepsia, 39, 167-174.

Wyman, J. F., Choi, S. C., Harkins, S. W., Wilson, M. S., & Fantl, J. A. (1988). The urinary diary in evaluation of incontinent women: a test-retest analysis. Obstetrics and Gynecology, 71, 812-817.

Yarnell, J. W., Voyle, G. J., Richards, C. J., & Stephenson, T. P. (1981). The prevalence and severity of urinary incontinence in women. Journal of Epidemiology and Community Health, 35, 71.

Yarnell, J. W., Voyle, G. J., Richards, C. J., & Stephenson, T. P. (1982). Factors associated with urinary incontinence in women. Journal of Epidemiology and Community Health, 36, 58.

Appendix A. Schedule of Measurements

	BL (pre-op)	Op	6 wks (post-op)	3m	6m	12m	18m	24m†
MESA	✓*			✓	✓	✓	✓	✓
H+P	✓**							
POP-Q	✓*				✓	✓		✓
Stress Test	✓				✓	✓		✓
PVR	✓				✓	✓		✓
Q-Tip	✓					✓		✓
UDS	✓							✓
Voiding Diary	✓*				✓	✓		✓
Pad Test	✓*				✓	✓		✓
Med. Audit	✓*			✓	✓	✓	✓	✓
Expectations of Surgery	✓*							
Resumption of Activities	✓			✓	✓			
QOL	✓*			✓	✓	✓	✓	✓
Sexual Function	✓*				✓	✓	✓	✓
Operative Measures		✓						
Satisfaction with Surgical Results				✓	✓	✓	✓	✓
Complications		✓	✓	✓	✓	✓	✓	✓
Pain←surgery			✓	✓	✓	✓	✓	✓
Incomplete Bladder Emptying			✓					
Readmission			✓	✓	✓	✓	✓	✓
New Interventions or Re-treatment			✓	✓	✓	✓	✓	✓

* Must be completed < 6 months prior to randomization. If surgery is delayed, these may have to be reassessed.

** Eligibility sections of History & Physical must be < 6 months prior to randomization. If surgery is delayed, these may have to be reassessed.

† Or at time of treatment failure, if earlier. If patient is surgically retreated and therefore has UDS prior to 24-months as part of the treatment failure battery, UDS are not done again at 24-months.

Appendix B. Complications of Surgery

A. Serious complications that mandate report to the DSMB within 72 hours:

1. Acute serious morbidity and mortality related to surgery: death; myocardial infarction; cerebrovascular accident; pulmonary embolus; renal failure; sepsis requiring admission to ICU; major anesthetic misadventure requiring admission to ICU.
2. Complications which contribute to serious morbidity on a subacute or chronic basis: abscess or infected hematoma that requires open or percutaneous intervention; injury to adjacent organ (injury to bladder, bowel, ureters, or vascular structures) which requires open, percutaneous, or endoscopic operations; fistula; nerve injury (specify site); deep venous thrombosis.

B. Complications of moderate or minor concern that are reportable to the DSMB at set intervals:

1. Complications which are of moderate concern and contribute to morbidity on a chronic basis: sling erosion; hernia; need for transfusion.
2. Short-term complications or minor complications: wound separation; hematoma, or seroma NOT specified above; atelectesis; pneumonia; cystitis or pyelonephritis (any antibiotics given for urinary tract symptoms); anesthetic minor complication (including aspiration pneumonia, laryngospasm, infection at catheter site); bladder injury.

C. Site-specific complications or deviations:

The DSMB must consider these complications in the light of individual surgeons and sites, including procedure-specific differences in primary outcome (cure of incontinence) and important but less serious complications (need for take-down.) A single surgeon or site that deviates significantly from the rest of the network should be evaluated for proficiency in that procedure, and consideration given to exclusion of data from that surgeon and/or site from final analyses.

Appendix C. Perioperative Measures

Preoperative Measures

- Adjuvant behavioral or biofeedback in previous 30 days: type and # sessions

Operative Measures

For both procedures:

- Date of surgery
- Surgery performed (1. Burch, 2. sling)
- More than one surgery; specify (List: enterocele repair, colpopexy, cystocele and rectocele repair, vaginal or abdominal hysterectomy, hernia repair; paravaginal repair; other)
- Assistant: Resident, Fellow, non-study surgeon – level and specialty
- Operative time: enter OR, start incision, wound closed, leave OR
- Type of anesthesia (LIST: 1. General, 2. Spinal, 3. Epidural, 4. Sedation, 5. Local, 6. None)
- Estimated blood loss: ____ ml as recorded by anesthesiologist
- Blood transfusion: #units, autologous (Yes, No)
- Suture material and gauge
- Intraoperative complications (e.g., urethral or bowel injury) [see Appendix B]
- Urine drainage: SP tube, urethral catheter, no catheter
- Cystoscopy: abnormal findings; describe intraoperative and corrected complications
- Was randomization violated, i.e., any deviation from randomized procedure

For Burch procedures

- Suture material and gauge
- Number sutures on each side
- Length of abdominal incision
- Orientation of incision: vertical, horizontal, other
- One vs. two passes through Cooper's ligament

For sling procedures

- Sling material: autologous fascia (rectus; if fascia lata, specify reason)
- Size of sling material: ____cm long x ___ cm wide
- Suture of sling material: simple one stitch, two stitches, helical x3, other
- Abdominal incision
  - Length of incision
  - Orientation of incision: vertical, horizontal, other
- Device to pass suture/sling from vagina to site of anchoring: specify device [LIST: Stamey needle, commercial device. If commercial device, specify name of device and brand.
- Folding of sling ends: Yes/No
- Tied suture over/to rectus fascia

Post-Operative Measures

- Complication(s): specify (see Appendix B)
  - In recovery room
  - First 24-hours after leaving recovery room
- Fever > 101°F, 38.3°C during hospitalization: specify
- Blood transfusion during hospitalization: # units, autologous (Yes, No)
- Length of hospitalization
- Audit of discharge medications
- Voiding at discharge
- Estimated residual urine volume
- Discharge with catheter: SP tube, urethral, clean self cath, none
- Pain

Perioperative Measures through 3 months

- Physician visits: number, reason
- Complications: specify
- Readmissions: date, reason, LOS for each
- Emergency room admissions: date, reason for each
- Additional abdominal or pelvic surgery: date, procedure, reason
- Medication Audit
  - Antibiotics: type, # days
  - Pain med: type, # days, # pills
- Resumption of spontaneous voiding
  - If catheter at discharge: date removed, residual urine volume at removal
  - If intermittent catheterization, when stopped
- Urine incontinence: frequency, type
- UTI: dates and treatment
- Persistent pain at site of surgery: duration, description
- Number of lost work days
- Resumption of normal activities

Measures for all Follow-up Points

- Persistent pain at site of surgery (i.e. >6months = "complication")
- Develop hernia: describe
- Develop vaginal prolapse: describe – POP-Q and self-report
- Develop new UI: describe
- Change in bowel movements: describe
- Develop new fecal incontinence: describe
- Develop new sexual dysfunction: describe

Appendix D. Guidelines for Post-Operative Instructions

ACTIVITY:

Rest as much as needed during the first two weeks after your procedure.
Avoid heavy lifting, pushing or pulling.
Lifting: Limit your lifting to about 10 lbs for the first 4-6 weeks post-op (About a gallon of milk).
Discuss heavier lifting with your doctor at your post-op visit.
Avoid standing for prolonged periods of time.
Climbing stairs is allowed.
Talk to your doctor about when you may resume usual physical activity.

NUTRITION:

Resume your normal diet.
Drink 6-8 glasses of non-caffeinated beverages daily.
Eat a well-balanced diet.

ELIMINATION:

It is important not to strain during bowel movements.
Narcotics tend to make you constipated.
Preventing constipation is easier than treating it!
Eat a high fiber diet (fruits, vegetables, and bran).
Take a stool softener once or twice daily.

If constipation should occur:
You may take a mild laxative (Milk of Magnesia).
Add fruit and bran to your diet.
Drink more liquids.
Call your doctor or nurse if you experience burning on urination or urgency frequency or you feel that you are unable to completely empty your bladder.

VOIDING:

Avoid bladder distension.
Void every 2-3 hours, whether you feel like you have to or not.
Your sensation of fullness may be altered by anesthetics, swelling or repositioning of a previously prolapsed bladder.
If additional bladder care is required, you will receive instructions from your doctor or nurse.

HYGIENE:

You may shower and wash your hair. If your incisions are closed, you may bathe unless your doctor tells you otherwise. Do not douche or use tampons until after your follow-up appointment.

FEVER:

If you feel feverish or have shaking chills, take your temperature. If your temperature is 100.4°F (38°C) or above, call your doctor. The fever may mean there is an infection.

ABDOMINAL INCISION CARE:

Clean the incision with water. Do not use a dressing unless the incision is draining or irritated. If you have small adhesive strips in place, and they do not fall off within 10 days, carefully peel off. Check your incision daily for redness, draining, swelling or separation of the skin. Call your doctor if you notice any of these.

VAGINAL DISCHARGE:

If you have vaginal incisions, you may have bleeding and vaginal discharge for several weeks. If it is heavier than a normal period, call your doctor. Keep track of when the bleeding began and how many pads you have used that day. If you are still bleeding, try to remember when your last period began. This new bleeding may be your period.

PERI-CARE:

Keep your perineal area (the area between the vagina and the rectum) clean and dry. Perform peri-care after every bowel movement and each time you urinate. You make take a sitz bath or sit in a tub of clean warm water when necessary, unless your doctor tells you otherwise.

SEXUAL INTERCOURSE:

If you have an incision in your vagina you should not have sexual intercourse until your doctor tells you otherwise at your post-op visit.

PAIN CONTROL:

Most surgical procedures are associated with some degree of pain.
Follow your doctor's instructions regarding pain medications.
Poorly controlled pain in the perineal or vaginal area may contribute to your inability to urinate or have a bowel movement because of muscle spasms.
You may also take acetaminophen (Tylenol) or ibuprofen (Advil or Motrin).
Avoid aspirin.
Your need for pain medication will decrease over time.
If pain is not relieved by the medication, or the pain gets worse, call your doctor, as this may be a sign of infection.