PRIDE
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PRIDE - Study Protocol

Program to Reduce Incontinence by Diet and Exercise (PRIDE)

an NIDDK-sponsored, multi-center, randomized, controlled clinical trial comparing incontinence improvement between groups randomized to a weight reduction program or control in overweight or obese women with urinary incontinence

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SIGNATURE PAGE

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1.0 BRIEF SUMMARY

PRIDE — The **Program** to **Reduce Incontinence** by **Diet** and **Exercise** is a multicenter, randomized, clinical trial evaluating weight reduction as a treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized in a 2-to-1 ratio to either a 6-month weight loss program (lifestyle and behavior change) or control group (instructional handouts and brief informational sessions on diet and exercise) and followed for 18 months. At baseline, all women will be given a pamphlet describing a self-administered behavioral treatment program for incontinence. At 6 months, a second randomization will be done among women who complete the weight reduction program to test whether a motivation-based weight maintenance program results in superior long-term weight loss at 18 months compared to a skill-based maintenance program. In a subgroup of 100 women, we will perform standardized urodynamic studies to explore the mechanism by which weight loss improves incontinence.

2.0 BACKGROUND AND RATIONALE

Urinary incontinence is a prevalent health condition in women and has a significant impact on quality of life. Over 13 million Americans, including 25% of reproductive age women and up to 50% of postmenopausal women, are affected by stress (involuntary loss of urine with coughing, sneezing, straining, or exercise), urge (loss of urine associated with a strong need or urge to void) or mixed incontinence (episodes of both types).[1-3] While incontinence does not lead to death,[4] it is associated with a profound adverse effect on quality of life,[2, 5-7] a 20-30% increased risk of falls and fractures,[8] a three-fold increased risk of nursing home admissions,[9] and over $16 billion in annual direct costs.[10]

Current incontinence treatment is not satisfactory. The first line of treatment typically used for both stress and urge incontinence is bladder training, toileting assistance, and/or pelvic muscle rehabilitation.[11-13] These behavioral approaches are only modestly effective, and in many cases, a second line of therapy is needed. Pharmacological therapy, primarily with anticholinergic medications, is frequently the second line of therapy for urge incontinence and results in a 15-60% reduction in weekly incontinent episodes. However, anticholinergic side effects are common and the medications must be taken chronically.[1, 14-16] Newer medications and reformulations of older drugs provide better tolerability, but long-term compliance remains low.[17, 18] Surgery is another highly effective second line treatment, but incontinence tends to recur over time and surgery is associated with discomfort, a prolonged recovery period, and

operative complications, particularly in obese women.[19, 20]

Obesity is a strong risk factor for incontinence. Among older women with incontinence, 65 to 75% are overweight or obese. Moreover, epidemiological studies suggest that obesity is a strong risk factor for urinary incontinence.[21-24] Over 50% of American women are overweight (body mass index (BMI) 25 to 30 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2), and the prevalence of obesity is dramatically increasing.[25-29] In addition to the impact urinary incontinence has on quality of life and morbidity, obesity itself contributes to over 300,000 deaths per year. It is associated with increased risk for heart disease, hypertension, diabetes, cancer, arthritis, respiratory disease and depression [30, 31] and has direct and indirect costs of over $100 billion per year.[32] Thus, women who are both overweight and incontinent are at high risk for negative health outcomes and impaired quality of life.

Weight reduction may be an effective treatment for incontinence. In observational studies, morbidly obese women (>45 kg above ideal weight) with incontinence who had dramatic weight loss after bariatric surgery (45-50 kg) had significant improvement in urinary incontinence.[33, 34] Similarly, positive results were obtained in a small prospective cohort study with overweight and obese incontinent women enrolled in weight reduction programs.[35] Six of six women achieving a weight loss of $\geq$5% had at least a 50% reduction in incontinence frequency compared to one of four women with <5% weight loss ($p = 0.03$)**.** A 3-month randomized trial of a very low calorie liquid diet program compared to no intervention among 42 overweight and obese women with incontinence resulted in an average weight loss of 14 kg in the intervention group. The frequency of incontinence episodes was reduced significantly among women assigned to the weight loss group.[36] Thus, even modest weight reduction may be a clinically feasible treatment option for incontinence and may, in addition, improve control of hypertension, hyperglycemia, hyperlipidemia, reduce the risk of developing type 2 diabetes,[37] and produce marked improvements in mood and quality of life.[38]

The importance of weight maintenance. If the hypothesis that weight reduction improves incontinence is correct, then maintaining improvement in incontinence will depend on maintaining weight loss.

Standard approaches to weight loss maintenance have focused on helping participants refine their weight reduction skills.[39] Advances that have improved the efficacy of weight loss maintenance, and that have been incorporated into standard maintenance programs, include increased physical activity,[40] ongoing contact with the therapist and weight loss group,[41, 42] and increased attention to problem solving skills.[43] Despite these

additions, weight regain still occurs and by 18 months most programs obtain average weight losses of only 5-6 kg.[44] Developing a more effective long-term weight loss intervention is the top research priority in the behavioral treatment of obesity[45] and is clearly needed if weight loss is to be a lasting treatment for incontinence.

3.0 CLINICAL TRIAL OBJECTIVES

3.1 Primary aims of PRIDE are to:

1. determine whether randomization to a weight reduction program results in greater reductions in frequency of incontinence episodes at 6 months compared to a control condition;
2. determine if randomization to a motivation-based weight maintenance program results in less weight regain compared to a skill-based maintenance program from the end of the weight reduction program (6 months) to the end of the weight maintenance program (18 months);

3.2 Secondary aims are to:

3. identify women who are most likely to experience improved continence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed).
4. determine if randomization to a weight reduction program results in greater improvement in continence from baseline to 18 months compared to a control condition and whether the motivation-based weight maintenance program results in greater improvement in continence from baseline to 18 months than the skill-based weight maintenance program or control condition.
5. randomization to a weight reduction program results in greater improvement in quality of life from baseline to 6 and to 18 months compared to a control condition.

3.3 Tertiary aims in a volunteer subset of 100 participants are to:

6. evaluate whether urodynamic measurements can identify women who are most likely to experience improved continence after weight reduction
7. investigate the mechanism by which weight loss improves continence

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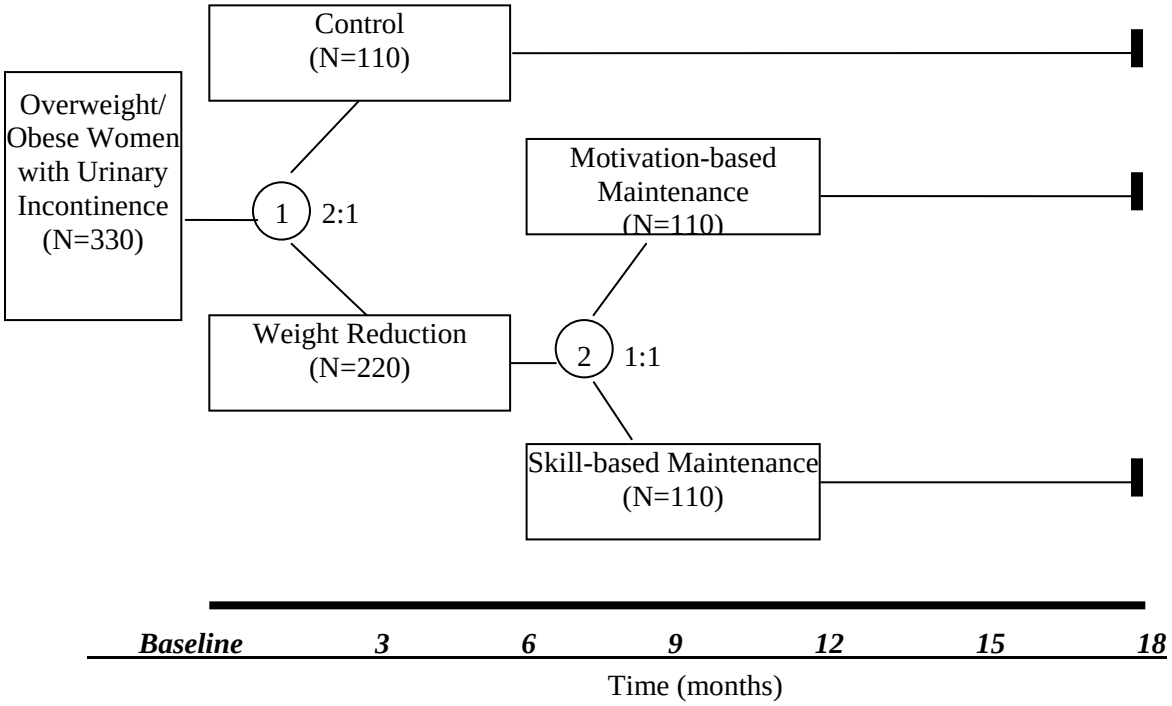
4.0 STUDY DESIGN

330 overweight or obese women with urinary incontinence will be randomized in a 2-to-1 ratio to either a 6-month lifestyle and behavior change weight reduction program or to a control condition (no weight reduction intervention) and followed for 18 months. At baseline, all women will be given a pamphlet describing a self-administered behavioral treatment program for incontinence (instructional booklet with voiding diaries, bladder training and pelvic muscle exercises). After completing the 6-month weight reduction program, women in this treatment arm will be randomized to either a motivation-based or a skill-based weight maintenance program. In a volunteer subgroup of 100 women, urodynamic studies will be performed at baseline and 6 months.

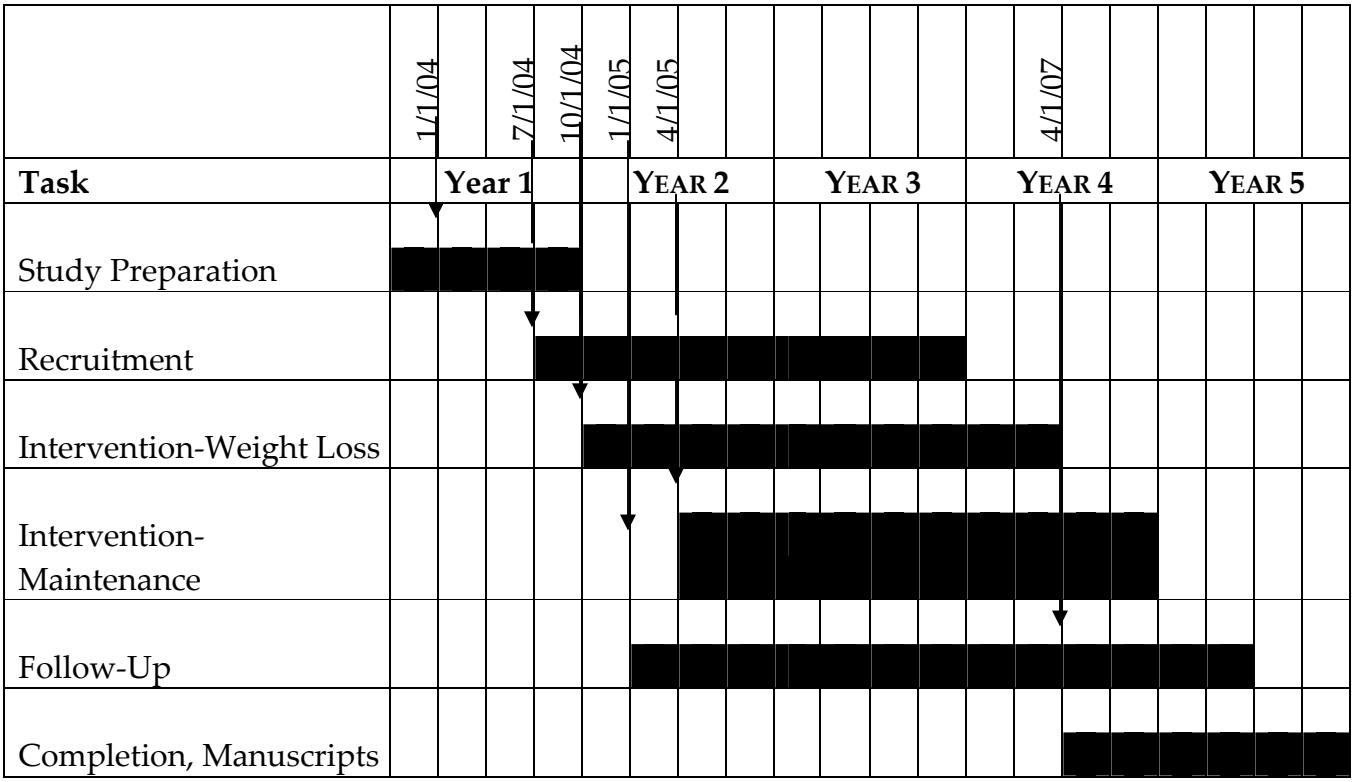


4.1 Study Timeline

The first 9 months of the study will include developing and refining the protocol, operations manual, forms, database, intervention materials and website. Participant recruitment will begin in the first year and continue through the end of the third year. Enrollment and intervention will begin in

year 2 and follow-up will be completed in mid-year 5. The final year of the study will include completing data collection and editing, data analyses, scientific presentations and manuscript preparation.

Project Plan:



5.0 STUDY SITES

The study will be conducted at two clinical centers: Miriam Hospital, Brown University, Providence, RI and the University of Alabama, Birmingham, AL. Data will be collected, managed and analyzed at the Women's Health Clinical Research Center, University of California at San Francisco, San Francisco, CA.

A list of investigators is available at the PRIDE public website at: http://coordinatingcenter.ucsf.edu/pride/

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6.0 STUDY POPULATION

6.1 Sample Size

A total of 330 overweight and obese women with urinary incontinence will be recruited (165 at each of 2 clinical centers).

6.2 Inclusion Criteria

1. women aged ≥ 30 years
2. not institutionalized
3. body mass index 25 to 45 kg/m^2
4. current urinary incontinence symptoms for ≥ 3 months by self-report and record ≥ 10 incontinent episodes per week at baseline on a 7-day urinary diary
5. able to complete a behavioral run-in consisting of self-monitoring of food and activity
6. report having a primary health care provider
7. able to understand and sign informed consent and complete baseline questionnaires
8. able to walk 2 blocks without stopping and without a cane or walker
9. agree not to initiate new treatment for incontinence or weight reduction, including behavioral, pharmacological or surgical therapies, for the duration of the study

Age and body mass index ranges were selected to identify a population most likely to respond to the intervention and safely able to participate in a behavioral weight loss program.

6.3 Exclusion Criteria

1. current use, or use within the previous month*, of medical therapy for incontinence or weight loss
2. pregnant or gave birth in the previous 6 months
3. urinary tract infection (dipstick urinalysis positive for leukocyte estrace, nitrites or blood) or report having ≥ 4 urinary tract infections in the preceding year

4. incontinence of neurologic or functional origin (by history)
5. report prior anti-incontinence or urethral surgery, pelvic cancer or pelvic irradiation
6. report significant medical conditions of the genitourinary tract (genitourinary fistula, interstitial cystitis, symptomatic pelvic organ prolapse)
7. report a medical condition that would affect the safety and/or efficacy of a weight management program involving diet and physical activity, including type 2 diabetes requiring medical therapy that may cause hypoglycemia, chronic steroid use or uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure > 100 mm Hg); women with a history of coronary heart disease may participate with written approval from their primary care physician
8. engaged in an active weight loss program and/or experienced a weight reduction of 10 lbs or more in the past 3 months
9. report conditions that, in the judgment of the clinical center Principal Investigator, render potential participants unlikely to follow the protocol for 18 months, including illness likely to be terminal within 2 years, plans to move, substance abuse, significant psychiatric problems, or dementia
10. participating in another research study that involves investigational drugs or can potentially confound the results of PRIDE

* Potential participants may be re-screened one month after stopping medical therapy for incontinence or obesity. Prior medical therapy for incontinence or obesity will not affect eligibility but participants will be asked not to initiate any treatment for incontinence or obesity during the study period except as directed by the study protocol.

7.0 ETHICS

7.1 Institutional Review Board

The study protocol, informed consent form, study questionnaires, educational and recruitment materials must be approved by the Institutional Review Board at each site and the coordinating center prior to the start of the study. Protocol amendments generated during the study must be approved by the IRBs prior to their implementation. Copies of all IRB approval letters will be sent to the Project Office at the NIDDK. Reports issued by the PRIDE Data and Safety

Monitoring Board will be distributed to the investigators to be forwarded to their IRBs. Any serious adverse events that occur during the trial must be reported to each IRB.

7.2 Informed Consent Form

Before individuals may participate in any screening procedures, informed consent for all phases of the trial must be obtained. The consent form will explain in lay language the goals of the study, the visits and procedures and the risks and benefits of participating. A separate protocol and consent form will be required for the 100 participants who volunteer for the urodynamic investigation. Any amendment to the protocol generated during the study that impacts participants will be reflected in a revised consent form that must be signed again by the participant.

8.0 STUDY SCHEDULE AND PROCEDURES

8.1 Summary of Study Visits

Measures	**OV**	**SV1**	**SV2**	**UDS**	**BL**	**3 mo**	**6 mo**	**12 mo**	**18 mo**
Describe study requirements	X								
Obtain Informed Consent	Y	Y							
Obtain physician consent		Y	Y						
7-day voiding diary		Y	Y		X	X	X	X	X
Measures	**OV**	**SV1**	**SV2**	**UDS**	**BL**	**3 mo**	**6 mo**	**12 mo**	**18 mo**
Dipstick urine analysis		Y	Y	X					
Height & Weight for BMI		Y	Y						
Weight					X	X	X	X	X
Waist Circumference					X		X	X	X
Blood Pressure		Y	Y				X	X	X
Demographic factors		Y	Y						
Medical/surgical/gynecological/incontinence history		Y	Y						

Training for diet & exercise diary, and completing questionnaires		Y	Y						
24 hour Pad Test			X				X	X	X
Incontinence questionnaire			X				X	X	X
Sexual function questionnaire			X				X	X	X
Bowel function questionnaire			X				X	X	X
Food Frequency Questionnaire			X				X	X	X
Motivation Questionnaires			X				X	X	X
Paffenbarger Activity Questionnaire			X				X	X	X
Sleep questionnaire			X				X	X	X
Incontinence Impact Questionnaire			X				X	X	X
Urogenital Distress Inventory			X				X	X	X
Short form 36			X				X	X	X
UI - Satisfaction measures			X				X	X	X
Beck Depression Inventory			X				X	X	X
Urodynamic assessment*				X			X		
Brinks Score, Pelvic, Q-tip & POP-Q exam*				X			X		

*Note: These measures are completed only on the first 50 women at each site to volunteer for more extensive testing.

Y = measurement can be completed at either screening visit

TS = Telephone Screen; OV=Orientation Visit; SV=Screening Visit; BL=Baseline Visit; UDS=UroDynamic Study Visit

8.2 Randomization Procedures

8.2.1 Randomization to Weight Loss or Control

Women will be randomly allocated in a 2-to-1 ratio to either the weight reduction program or control condition. Randomization will be stratified by clinical center. Blocked randomization within each of the centers will then be performed to ensure that the number of participants in the two treatment groups is close to our goal of an exact 2 to 1 ratio. Since the intervention is not strictly blinded, block size

will vary randomly from 3 to 6 in a schedule that is not known to investigators. In addition, to assure an even distribution of treatment groups, a separate set of randomization envelopes will be prepared, as described above, for women who choose to have the urodynamic assessment. Thus, the randomization will be stratified both by center and whether or not the participant volunteers for the urodynamic assessment.

Using computer algorithms for a 2 to 1 randomization, Coordinating Center staff will prepare two sets of sealed, opaque envelopes for each clinical center, color coded for urodynamic assessment or no urodynamic assessment. On the outside, the envelopes will be numbered consecutively with the randomization sequence number; on the inside the envelopes will contain study group assignment. When eligibility has been confirmed by completion of the eligibility checklist, clinical center staff will enter the date, participant's name, and study ID (assigned at the screening visit) consecutively in a randomization log, select the next numbered randomization envelope from the appropriate color-coded series, enter the randomization sequence number listed on the outside of the envelope, then open the envelope and enter the study group assignment contained inside the envelope on the randomization log. All opened and unopened envelopes will be retained at the clinical center for review during study site visits and at the end of the trial. Randomization dates and times should follow the order of the randomization sequence numbers, providing a check on validity. Screening data will be retained by study ID for women not randomized, facilitating review of the recruitment process.

8.2.2 Randomization to Motivation-based or Skill-based Weight Maintenance

After 6 months of weight reduction intervention, women in the weight reduction group will be cluster randomized by weight reduction group, with equal probability of the group being assigned to either motivation-based or skill-based weight maintenance strategies. Clustered randomization will introduce some complexity in the analyses. However, we believe this problem is outweighed by the support and enthusiasm that typically develops among the 10-20

women in each weight reduction counseling group who have been working together to lose weight for 6 months. Blocked randomization within each center will be done to ensure that the number of participants is equally distributed between the maintenance strategies. Since the intervention cannot be easily blinded, block size will vary randomly from 2 to 4 groups in a schedule that is not known to investigators. For each clinical center, a set of opaque envelopes containing treatment assignment for each weight reduction group will be prepared by the Coordinating Center. Each weight reduction group will be numbered during the weight reduction intervention. At the end of the weight reduction intervention, the number of each group will be entered on a randomization log, and the next consecutive envelope will be opened to determine treatment assignment. This treatment assignment will be entered in the randomization log for each member of the weight loss group.

8.3 Study Visits

8.3.1 Recruitment Phase

Women will be recruited by (1) direct, community-based efforts using large media (newspaper notices, television ads, etc) and small media (brochures in local businesses, talks to local community, notices in churches, salons etc); (2) seeking referrals from physician's offices (specifically in gynecology, primary care, and geriatric medicine) and (3) purchasing targeted mailing lists. Every effort will be made to assure significant representation of minority women by working with key community leaders, building trust and gaining support, as well as providing community education about the nature of the health problems addressed within the project (incontinence and obesity). Transportation and parking costs may be reimbursed and participants will be provided a stipend for attending assessment visits. The individual clinical centers will be responsible for recruiting the required number of subjects and the Coordinating Center will provide centrally developed recruitment materials. The Coordinating Center will monitor recruitment at each clinical center on a real-time basis, lead periodic conference calls about recruitment and retention, and provide regular reports to the Steering Committee, Data and Safety

Monitoring Board and the NIDDK.

8.3.2 Screening Visits

Women who respond to study advertisements will be called on the telephone, provided a general overview of the study and, if interested, will complete a brief survey to determine initial eligibility. Eligible respondents may be invited to attend a group Orientation Visit where the purpose, study schedule and informed consent document will be described briefly, questions answered, and general eligibility and interest level assessed. Interested participants will be invited back for a Screening Visit 1 (SV1) where the study will be explained in detail, informed consent will be obtained, and confirmatory measures of eligibility will be performed (weight, height, blood pressure, urine analysis). Participants will be trained to keep 7-day diaries of food intake, physical activity, and voiding and will be given baseline questionnaires assessing incontinence severity and distress, dietary intake and physical activity patterns. These will be completed at home and returned at Screening Visit 2 (SV2). After a 1-2 week period has elapsed, participants will return to the clinical center for SV2, where the diaries and questionnaires will be reviewed for completeness and eligibility. (Height, weight and blood pressure should be performed at this visit if they were not done at SV1.) Repeat blood pressure measurements are allowed at this visit if the participant failed the eligibility criterion at SV1. To be eligible, participants must record having had at least 10 episodes of incontinence during the prior week on the voiding diary. Eligible participants will be given a new 7-day voiding diary, the 24-hour pad test kit, and the self-administered health assessment and motivation questionnaires to complete at home. The pads will be mailed back to the clinic and the questionnaires and diaries should be returned at the Baseline Visit (BL). Urodynamic testing procedures will be discussed.

8.3.3 Urodynamic Study Visit

To explore mechanisms by which weight loss may result in improved continence, 50 volunteers at each site will be scheduled for a Urodynamic Study visit (UDS) prior to randomization and at Month 6.

To ensure equal distribution of participants across treatment groups the 100 volunteers will be randomized separately as described in Section 8.2.1. At this visit, Pelvic Organ Prolapse Quantification (POP-Q), urethral hypermobility (Q-tip test), Brink's score of pelvic muscle strength and urodynamic studies including passive uroflowmetry, filling cystometrogram, and cough stress test studies will be performed. Measurements, diagnoses, and terms will conform to the recommendations of the Committee on Standardization of Terminology of the International Continence Society and will use the same methods as the NIDDK-funded Urinary Incontinence Treatment Network.[46] The POP-Q is a standardized description of the severity of pelvic organ prolapse with good inter- and intra-observer reliability for prolapse staging.[47-50] Mobility of the urethra and bladder neck will be evaluated using the Q-tip test, with bladder neck hypermobility defined as a resting angle >30^{o} or maximum straining angle >30^{o}.[51, 52] The Brink's test assesses pelvic muscle strength by scoring perceived pressure on the examiner's finger, alteration of the vertical plane, and contraction time. [53] The urodynamic measures have been demonstrated to be reproducible, to correlate with each other, and to correlate with clinical measures of incontinence severity.[54-57] These measures will be used to identify women who are more likely to have improvement in continence due to weight loss and to explore mechanisms by which weight loss might improve continence. We will perform these tests in a subset of participants because these tests are expensive and invasive, and our hypotheses regarding how weight loss may affect continence are exploratory.

8.3.4 Randomization/Baseline Visit

At the randomization/baseline visit, weight and waist circumference will be measured and the second 7-day voiding diary will be reviewed. The following self-administered questionnaires will be reviewed for completeness: Food Frequency Questionnaire, motivation questionnaires, Paffenbarger Activity Questionnaire, Incontinence Impact Questionnaire, Urogenital Distress Inventory, Short Form 36, Beck Depression Inventory and Health Satisfaction rating. All participants will be given the urinary incontinence self-administered behavioral training booklet. Pads distributed at SV2 will be weighed as

soon as they are received at the site. The list of inclusion and exclusion criteria will be reviewed and participant eligibility will be confirmed. At the end of the visit, study staff will select the next envelope from the set of color-coded randomization envelopes, the envelope will be opened and the treatment group recorded as described in Section 8.2.1.

8.3.5 Follow-Up Visits

At 3 months, participants will attend a visit at the clinical center for weight measurement and review of the 7-day voiding diary. At 6, 12 and 18 months, participants will be seen at the clinical centers to repeat weight, waist circumference, pad test, self-administered health assessment questionnaires and the diet, exercise and voiding diaries. The 7-day voiding diary, pad test kit, diet and exercise diaries and questionnaires will be mailed to participants 3 weeks before the follow-up visits. Participants will complete these measures at home and return them at their visit to be reviewed by study staff. Participants will be asked to bring to the visit all prescription and non-prescription medications that they are currently taking and these will be recorded.

8.4 Measures

8.4.1 7-Day Voiding Diary

Voiding diaries serve as the primary outcome instrument to measure change in symptoms of urinary incontinence. The diary includes frequency of micturitions (diurnal and nocturnal) and incontinence episodes classified by clinical type (urge, stress, other) along with time of occurrence. Simple written instructions and a sample of a completed diary will be given to participants. Study staff will review instructions for completion of the diary with the participant to ensure proper understanding. All participants will complete voiding diaries at each assessment point and diaries will be given or mailed to the participant prior to the visit. Participants will be asked to bring the completed diary with them to the visit. The clinic staff will review diary entries for completeness, summarize the information and fax the summary data into the database. Copies of the diaries will be sent to

the Coordinating Center where staff will perform the same summarization, entering the summary data into the database as a quality control check of the primary outcome variable.

8.4.2 24-Hour Pad Test

Pad testing will be used to quantify the amount of urine lost involuntarily and will reflect everyday incontinence. This standardized test[46] correlates well with incontinence symptoms, and has good reproducibility. The 24-hour pad test includes simple written instructions, pads, plastic storage bags and addressed, stamped envelope to return the pads to the clinical site. Study staff will review instructions for completion of the test with the participant to ensure that she understands how to properly complete the test. Every effort will be made by study staff to encourage participants to fully complete the test by collecting all pads. All participants will complete 24-hour pad tests at each assessment point. A secondary outcome of this study is the change from baseline in pad weight for a 24-hour pad collection at the 6, 12 and 18-month follow up.

8.4.3 Incontinence Questionnaire

The incontinence questionnaire is a self-report measure of incontinence severity. It includes the 2 Incontinence Questions (2IQ), American Urological Association Symptom Index (AUA Symptom Index), Sandvik Severity Index, and Incontinence Expense Questionnaire. The 2IQ is a short questionnaire to diagnose the type of urinary incontinence in women. It is currently being studied in a multi-site study to compare the accuracy of the 2 -IQ compared to a standard extended evaluation for diagnosis of incontinence type (Diagnostic Aspects of Incontinence Study; Coordinating Center PI: D. Grady). We have added a third question to assess bothersomeness of each type of incontinence. The AUA Symptom Index and the Sandvik Severity Index are validated instruments to assess lower urinary tract and incontinence symptoms, respectively. For the Incontinence Expense Questionnaire, participants to record resources used in an average week specifically for incontinence (pads, protection, laundry, dry cleaning). A generalizable cost for the resources is then estimated

by multiplying resources used by national resource cost estimates.

8.4.4 Sexual Function Questionnaire

The sexual function questionnaire is a self-report survey of sexual activity, satisfaction with sexual activity and four sexual function domains (interest, ability to relax, arousal and orgasm).

8.4.5 Bowel Habits Questionnaire

The Bowel Habits Questionnaire is a self-report survey to assess bowel function and habits, including frequency, consistency, straining with bowel movements, constipation, fecal and flatal incontinence. The questionnaire was developed from often-used instruments, including the ROME II criteria, Gastrointestinal Quality of Life Index, and **scoring system for the assessment of bowel and lower urinary tract symptoms in women.** The Bowel habits Questionnaire in PRIDE underwent extensive pretesting and is currently being validated in the Reproductive Risks for Incontinence Study at Kaiser (RRISK).

8.4.6 Weight, Height and Body Mass Index

Weight will be recorded in kilograms using a calibrated scale. Participants will be measured in light clothing (without shoes) to the nearest 0.5 kg. Standing height, which is measured at the screening visit only, will be measured in millimeters with a wall-mounted Harpenden stadiometer. Body mass index will be calculated from body weight and height as weight in kg divided by the square of height in meters. Body mass index will be used to verify study eligibility.

8.4.7 Waist Circumference

Waist (abdominal) circumference is an anthropometric indicator of deep adipose tissue. Measurements will be done over bare skin or underwear using a flexible, inelastic fiberglass tape measure marked in centimeters. Waist circumference will be measured at the minimum circumference, usually the umbilicus, between the iliac crests and

lower ribs.

8.4.8 Food Frequency Questionnaire

Food intake will be assessed using a self-administered Block food frequency questionnaire to allow quantification of total energy intake and percent calories from fat. These data will be used to estimate dietary change and to provide information about adherence of participants to the weight loss program.

8.4.9 Physical Activity

The Paffenbarger Activity Questionnaire[58] will be administered as a measure of physical activity. This questionnaire has been used to assess leisure time activity in many studies and can be scored to provide an estimate of calories expended per week in overall leisure time activity and in activities of light (5 kcal/min), medium (7.5 kcal/min), and high (10 kcal/min) intensity. Changes in exercise on the questionnaire have been shown to be predictive of weight change in overweight and obese individuals. Physical activity will be used to characterize adherence to the weight loss intervention and will be examined as a potential predictor of successful weight maintenance.

8.4.10 Sleep Questionnaire

We will assess sleep quality using established and validated instruments, the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness using the Epworth Sleepiness Scale (ESS) that are the standard for sleep research. The PSQI is a 19-item questionnaire that measures reported sleep patterns and sleep problems, including sleep quality, sleep latency, sleep efficiency and napping behavior.

8.4.11 Quality-of-Life Measurements

Incontinence Impact Questionnaire

The Incontinence Impact Questionnaire is a validated instrument that measures the impact of incontinence on social activity, physical

activity, travel, and emotional health on a 4-point Likert scale, with the sum of responses transformed into a score on a 0-100 continuous scale.

Urogenital Distress Inventory

The Urogenital Distress Inventory is a validated instrument that has been used extensively in incontinent populations to quantify incontinence symptom bothersomeness.[59] The degree of bothersomeness of irritative, obstructive/discomfort, and stress symptoms is recorded on a 4-point Likert scale with the sum of responses transformed into a score on a 0-100 continuous scale.

Short Form 36

The Short Form 36 is a 36-item measure that was drawn from the 149-item full set of the Medical Outcomes Study (MOS) Functioning and Well-Being Profile.[60, 61] Two summary scales can be calculated, the physical component summary and the mental component summary.[61] The physical component summary subscale addresses the areas of greatest importance to women with both incontinence and overweight and obesity. Large differences in change scores on this subscale have been observed when overweight and obese women reduce weight[62, 63] and with improvement in incontinence severity.

Participant satisfaction with health

We will include a rating of satisfaction with changes in incontinence used in prior incontinence treatment studies.[35, 36] This is a self-report ordinal scale and measures how participants feel about their treatment outcomes.

Beck Depression Inventory

The Beck Depression Inventory [64] is a 21-item self-reported measure of depressive symptoms. It will be used in our study to assess changes in depressive symptoms related to randomization to the weight loss intervention, to the motivation-based weight maintenance program, and to changes in weight and frequency of incontinence.

8.4.12 Other Measurements

Variables that may act as predictors or moderators of the efficacy of weight reduction for reducing the frequency of incontinence will be documented at baseline. These covariates include demographic characteristics (age, race/ethnicity, relationship status, education, annual family income), general health, genitourinary history (duration of incontinence, prior type and duration of therapy, amount of urine loss, pad use, drinking habits), reproductive health (gravity, parity, route of delivery, menopause status, hormone therapy use), medical history (hypertension, pulmonary disease, stroke, diabetes, surgical history (hysterectomy, pelvic organ prolapse repair, other pelvic or abdominal surgery), and medications.

8.4.13 Ensuring Objective Assessments

Throughout the study every effort will be made to ensure objective and blinded assessments of outcomes. Although participants will be told the name of their treatment assignment they will not be provided details about the intervention techniques of the other treatment groups. Focus will instead be maintained on the support group to which they are assigned.

Staff who review the voiding diaries and record participant weight at the 6, 12 and 18 month assessments will not be informed of the participant's treatment assignment and will not participate in the delivery of the study interventions. Likewise, staff who perform the urodynamic studies will not be informed as to the participant's treatment assignment. Care will be taken to avoid overtly identifying treatment assignments on participant charts.

9.0 Study Interventions

9.1 Incontinence Information

At the randomization visit, <u>all</u> participants will receive a booklet that includes information commonly given to incontinence patients in clinical practice entitled "Staying Dry: A Practical Guide to Bladder Control - Patient

Instruction Booklet". The booklet presents information about urge and stress incontinence, how to locate the pelvic floor muscles, daily pelvic floor muscle exercises, use of pelvic muscles to avoid urine loss and strategies for managing symptoms of urinary urgency.

9.2 Education for the Control Condition

In addition to the incontinence self-help booklet, women randomized to the control condition (entitled the "Structured Education Program"), will be invited to participate in hour long group educational sessions at weeks 2, 4, 6 and 8. At months 6, 9 and 15, the groups will meet again for informational sessions. The content of these education and support sessions will include information about weight loss, physical activity, healthy eating habits and general health promotion.

9.3 Weight Reduction Program (Months 1-6)

Participants in the weight reduction program (entitled the "Lifestyle and Behavior Change Program") will receive an intensive group-based behavioral weight reduction program. They will be taught specific cognitive and behavioral skills to assist in the modification of their eating and exercise habits. Participants will meet weekly for 6 months in group-sessions led by a nutritionist, exercise physiologist, or behaviorist and will follow a structured protocol. Therapists will not discuss incontinence during the weight reduction program. With this intervention, women are expected to lose an average of 7-9% of their initial body weight in 6 months. The central components of the weight loss program are:

Diet: All participants will be placed on a standard caloric diet (e.g., 1200-1500 kcals/day, depending on initial body weight). The dietary recommendations in this study (< 30% of calories from fat; < 10% of calories from saturated fat) are consistent with the recommendations of the American Heart Association, the American Diabetes Association, and the American College of Sports Medicine.[65-67] To help participants initially meet their calorie and fat goals, sample meal plans modeling appropriate food selections will be provided and meal replacement products will be

recommended and/or provided to participants. A fat/calorie guidebook will also be given to each participant to be used in the self-monitoring of food intake. Participants will be instructed to monitor food and beverage intake daily.

Exercise: All participants will be encouraged to gradually increase their physical activity until they are exercising 40 minutes per day on 5 days per week. Participants will be encouraged to exercise on their own at home using brisk walking or activities of similar intensity to brisk walking as their primary form of physical activity. Since lack of time is considered the greatest barrier to exercise, participants will be encourage to accumulate the amount of exercise necessary each day by engaging in multiple short bouts of activity (e.g., at least 10 minutes in length). Participants will be instructed to self-monitor their exercise daily. Pedometers will be provided and participants will be encouraged to gradually increase their activity to 10,000 steps per day.

Behavioral Skills: To encourage the adoption of the above dietary and physical activity recommendations, the following skills will be introduced in the initial phase of treatment:

- *Self-monitoring*
- *Stimulus control*
- *Problem-solving*
- *Assertiveness training*
- *Social support*
- *Goal setting*
- *Cognitive restructuring*
- *Relapse prevention*

9.4 Weight Maintenance Interventions (Months 7-18)

After 6 months of weight reduction intervention, women in the Lifestyle and Behavior Change Program will be cluster randomized at each site by weight reduction counseling group to a skill-based or motivation-based weight

maintenance program. Both 12-month maintenance programs will involve group meetings every two weeks. The programs will be matched on contact frequency and duration. The programs will differ in their treatment focus.

9.4.1 Skill-Based Approach to Maintenance

The skill-based approach is similar to what is commonly taught in the maintenance phase of standard behavioral weight loss programs. In the skill-based group, months 7-18 of treatment will focus on refining the cognitive and behavioral skills acquired in the first 6 months of treatment. Topics presented in the first 6 months of treatment will be revisited, expanded and refined. The overall goal will be to practice the skills acquired in the first 6 months of treatment so they increasingly become "habits" and to help participants apply these skills in a variety of situations that will occur over the year of maintenance.

9.4.2 Motivation-Based Approach to Maintenance

The focus of treatment in the motivation-based group in months 7-18 will be to increase and sustain motivation to utilize the dietary, physical activity, and behavioral skills already acquired. Group sessions will be devoted to the introduction and discussion of exercises designed to 1) increase participants' satisfaction with their weight loss and incontinence outcomes, 2) decrease participants' ambivalence about their current behavior change efforts, 3) increase participants' investment in behavioral choices, and 4) increase participants' motivation to maintain their new eating and exercise behaviors. Examples of specific group topics and exercises are:

- *Personalized reminders of baseline state*
- *Motivational interviewing*
- *Personal investment in new behaviors*
- *Self-reward*

9.5 Retention of Study Participants

Every effort will be made to retain participants through the 18-month follow-up period. Based on prior experience at the two Clinical Centers, we expect 95% (or 314) of the 330 women to complete the 6-month assessment and 85% (n=280) of participants to complete the 18-month assessment.

The investigative team will encourage retention in PRIDE by educating participants about the importance of the study, encouraging excellent staff-participant rapport, and promoting participant loyalty and identification with PRIDE. Birthday and anniversary notices will be sent and friendly and efficient Clinical Center environments will be maintained. Identifying information including address, phone number, social security number and the name, address and phone number of one family member and two close friends able to locate the subject will also be obtained prior to randomization to facilitate participant-staff contact. Identification with PRIDE will be promoted via the periodic newsletter, refrigerator magnets with the PRIDE logo, and an annual social event for study participants. Participants will be given a stipend of $25 at both 6 and 12 months and $50 at 18 months for completing these assessment visits. The coordinating center will monitor the retention rate at all clinics, identifying problems, proposing solutions, and reporting on these matters to the Steering Committee and to the Data and Safety Monitoring Board.

10.0 SERIOUS ADVERSE EVENTS

The diet and exercise intervention in PRIDE was designed to encourage gradual weight loss in the context of a healthy lifestyle and should pose no added risk to overweight or obese participants. Only serious adverse events as defined by the Food and Drug Administration (death, life-threatening event, inpatient hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity) will be routinely ascertained in this trial. Important medical events may be considered serious adverse experiences at the discretion of the site Principal Investigators if they might jeopardize the participant or might require medical or surgical intervention to prevent one of the outcomes defined as serious.

Safety-related events will be reported in a timely fashion as required by the Data and Safety Monitoring Board and the IRB.

11.0 DATA MANAGEMENT

11.1 Data Collection

The Coordinating Center will develop machine-readable data forms using Cardiff Teleform software. Data forms will be filled out at the clinical sites and sent to the Coordinating Center (CC) via standard fax machines. At the CC, the forms will be received on a server that will use optical character reader (OCR) technology to acquire the data. A CC operator will verify the data manually on screen. This important step corrects many misinterpretations in the automated data input. Verified data are then sent over the local area network (LAN) at the CC to a database on a Microsoft SQL Server. Analog images of the forms are stored in an image-management system on optical disk. The CC does not receive any paper in the process of data acquisition.

11.2 Data Processing

All of the study data are subject to a set of daily error-checking programs. This routine includes checks for completeness, data consistency, and invalid ranges. The results are posted to the study website where clinical site personnel check daily to confirm that the CC has received all of the faxed forms and to address any queries.

A password-protected web site will be the study's data collection hub. Computers at the clinical centers will access a secure and private UCSF CC web server that provides continually updated data summary reports. All reports available on the website will be generated on demand in real time from current study data. The Coordinating Center will provide user accounts and security-enabled web browsers for all clinical center staff.

Clinical centers will respond to queries and edit data forms on the website. As part of the data editing system, the website will also include pages that closely resemble the questionnaires so that clinical staff can view the data that has been accepted into the data system.

Clinical sites will access their data via these pages and address queries. Access to these pages will be restricted to authorized personnel.

12.0 STATISTICAL ANALYSIS, SAMPLE SIZE AND POWER ESTIMATES

12.1 General Analysis Considerations

12.1.1 Analysis Strategy

The primary analyses will be by intention-to-treat, without regard to adherence to intervention protocols. The major outcome for several of the specific aims are change from baseline in frequency of incontinence episodes, body weight or quality of life. Our primary analysis approach will use mixed linear regression models [68, 69] to compare the average changes in the intervention and control groups. We will control for Clinical Center as a fixed effect in all analyses. Interactions of the outcomes with Clinical Center will be assessed in exploratory analyses.

12.1.2 Cluster Effects

Weight loss groups of 10-20 women will be assembled immediately after randomization and preserved in the second randomization, by group, to motivation-based or skill-based maintenance. There may be correlation of outcomes for members of these groups that would reduce precision and power, increasing sample size requirements. This can be summarized as the design effect, or the ratio of the required sample size to the sample size that would be needed if there were no correlation of outcomes within small groups. Mixed linear models will be used to account for correlations within intervention groups. Fit by restricted maximum likelihood and implemented in SAS Proc Mixed, this method is powerful and accommodates the complex covariance structures that will arise, which will differ by treatment arm. It is also robust to moderate departures from multivariate normality,[70] but normalizing transformations of the outcome variables will be developed as necessary.

Potential complications due to dropout. In studies of weight loss, participants who drop out early typically regain most or all the lost weight. Under the hypotheses motivating this study, this would imply that most or all improvements in incontinence will also be eroded

among study dropouts. The first line of defense in this trial will be to minimize the dropout rates, and to attempt to obtain outcome measurements on participants who are no longer participating in the weight loss intervention. In addition, current practice in weight loss studies is to impute baseline outcomes for observations missing due to dropout, substantially reducing bias due to "non-ignorable" missingness.[71, 72] A slight drawback of this procedure is that such singly imputed values are treated as known, so that standard errors on average are too small. To address this potential source of inferential error, we will use multiple imputation of the baseline outcomes with an additive error term derived from the repeated measures model estimate of within-subject residual error. The analysis will then be carried out in the multiple datasets, and the results combined using standard methods to produce summary effect and standard error estimates that properly incorporate the imputation error.[71, 72] As a sensitivity check, we will also carry out a secondary analysis without imputation, but adjusted for baseline covariates, under the assumption that the data are missing at random [71] given treatment assignment, the observed outcome values, and baseline predictors of outcome.

12.2 Statistical Methods

12.2.1 Specific Aim #1

To determine whether randomization to a weight reduction program results in greater reductions in frequency of incontinence episodes at 6 months compared to the control condition.

Analysis. Our hypothesis is that randomization to the weight reduction group will result in greater reductions in frequency of incontinence compared to the control group. The predictor variable is assignment to the weight loss or control group and the outcome is change from baseline to the end of the weight loss intervention at 6 months in number of incontinent episodes per week, as recorded on the 7-day voiding diary. As described above, we will use mixed linear regression models to compare average changes in the intervention and control groups, controlling for clinical center and taking account of clustering within weight loss groups.

Sample size estimation. In our pilot study of weight loss for treatment of incontinence, the between-group difference in reduction in incontinence frequency was 12 episodes per week (average reductions of 14 vs 2 episodes in the weight loss vs. control groups), with standard deviation (SD) of 14 episodes per week, for a very large standardized effect size of nearly 0.9 SDs. In the proposed study, expected weight loss will be smaller and the control group will receive a self-help booklet that will likely result in some improvement in incontinence; furthermore the pilot study was small, providing imprecise estimates. Thus, we conservatively assume a smaller net reduction in incontinence frequency of 6 episodes per week in the weight reduction compared to the control group, half the effect seen in the pilot study but large enough to be clinically meaningful. This corresponds to a standardized effect size of .43 SDs, assuming an SD of 14 episodes per week for the changes in frequency. We also assume that 10% of the sample will drop out before the 6-month visit; with imputation of baseline values for missing post-randomization incontinence frequencies, this attenuates the effect size in proportion to the dropout rate. Finally, we assume that clustering within the small intervention groups will induce a moderate design effect of 1.3. We adapted standard methods for two-sample comparisons of a continuous outcome to account for the design effect as well as the attenuation of the treatment effect size by imputation of baseline values. Under these assumptions, a sample of 330 women will provide at least 80% power in two sided tests with alpha of 5% to detect between-group differences of 6 incontinence episodes per week. Small to moderate gains in power may be obtained by the use of repeated measures, depending on the level of within-subject correlation.

12.2.2 Specific Aim #2

To determine if randomization to a motivation-based maintenance program results in less weight regain from 6 to 18 months compared to a skill-based maintenance program.

Analysis. Our hypothesis is that motivation-based weight maintenance will result in less weight regain than skill-based weight maintenance over the 12 months of the intervention. The predictor variable is random assignment to the motivation-based weight maintenance program

compared to skill-based weight maintenance or control group, and the outcome is change in weight from the end of the weight reduction program at 6 months to the end of the maintenance period at 18 months. As in Specific Aim #1, we will use mixed linear regression models for change in weight over the maintenance period, controlling for group, degree of weight loss during the weight loss period, and taking account of clustering by weight loss group.

Power estimates. Conservatively assuming a loss to follow-up of 15% between 6 and 18 months, the sample of 220 women randomized to motivation-based or skill-based maintenance strategies will provide 80% power to detect between-group differences in weight loss of 0.56 standard deviations. In prior TRIM weight loss studies,[73] the standard deviation of weight loss at 18 months in the skill-based behavioral treatment condition was 6.8 kg, so that the minimum detectable between-group difference in average weight loss at the end of the study will be less than 3.8 kg.

12.2.3 Specific Aim #3

To identify women who are most likely to experience improved continence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed).

Analysis. Our hypothesis is that some subgroups of women (defined by baseline body weight, body mass index, waist circumference, or type of incontinence), will be more likely to have improvement in incontinence with weight loss compared to others. Analyses in subgroups defined by these baseline variables will be similar to those described for Specific Aim #1. These subgroup analyses constitute comparisons between randomized groups, and are only mildly affected by the multiple comparisons problem. We will test for subgroup by treatment interactions.

Power estimates. Under the same assumptions used for Specific Aim 1, subgroups comprising 50, 40, or 30% of the sample will provide 80% power to detect standardized effects of approximately 0.58, 0.63, and 0.75 SDs, respectively, corresponding to changes of 8.5 to 10.5 episodes

of incontinence per week.

12.2.4 Specific Aim #4

To determine if randomization to a weight reduction program results in greater improvement in continence from baseline to 18 months compared to control and whether the motivation-based maintenance program results in greater improvements in continence than the skill-based maintenance program or control from baseline to 18 months.

Analysis. Our hypotheses are that the weight reduction program will result in lower frequency of incontinence overall than in the control condition, and that motivation-based weight maintenance will result in lower frequency of incontinence than skill-based weight maintenance during the 18 months of follow-up. The predictor variables are random assignment to the weight reduction program or to the motivation-based weight maintenance program compared to skill-based weight maintenance, or to the control group, and the outcome is change from baseline to the end of the weight loss intervention at 18 months in frequency of incontinence episodes. Analyses will be similar to those described above for specific aim 1.

12.2.5 Specific Aim #5

To determine if randomization to a weight reduction program results in greater improvement in quality of life from baseline to 6 and 18 months compared to the control condition.

Analysis. Our hypothesis is that randomization to a weight reduction program will result in greater improvements in quality of life measures than to a control condition at both 6 and 18 months of follow-up. The predictor variable is assignment to the weight reduction or control groups and the outcome is change in quality of life outcomes including Incontinence Impact Question (IIQ), Urogenital Distress Inventory (UDI) and Short Form-36 (SF36), from baseline to 6 and 18 months. Analyses will be similar to those described above for specific aim 1. In addition to the primary analysis comparing weight reduction to a control condition, we will also make pairwise comparisons between

motivation-based maintenance, skill-based maintenance, and the control condition at 18 months.

Power estimates. Under the assumptions used for Specific Aims 1 and 2, the sample of 330 women will provide 80% power to detect actual treatment differences of 0.43 SDs in the primary comparison between weight loss and control at 6 months, and 0.49 SDs at 18 months. In pairwise comparisons between the three groups at 18 months, we will be able to detect differences of 0.56 SDs. These are small to moderate differences, as shown below.

Instrument	SD of single measures	Minimum detectable difference in changes**
UDI	50[59]	22-28
IIQ	60[59]	26-34
SF36 PCS*	25-30[63]	16-18
BDI	4.5[74]	19-25

* Physical component scale

** Assuming within-subject correlation of repeated measures of 0.5

In all cases, smaller between group differences in change would be detectable if within-subject correlation exceeds 0.5.

12.3 Exploratory analysis of potential mechanisms for improvement in incontinence with weight loss.

A series of closely related mixed linear models will be used to assess mechanisms by which the weight reduction intervention potentially affects measured incontinence frequency as well as related quality of life measures. We will first assess modification of the effects of treatment by baseline urodynamic measurements of leak point and intravesical pressures, to determine if the effectiveness of the weight reduction intervention varies by these parameters. To maximize efficiency, effect modification will be assessed as a continuous interaction between treatment assignment and the urodynamic measures. We will then examine the overall effects of assignment to the weight reduction group on the urodynamic measures as well as weight loss, to show

the effect of the intervention on the proposed mediators. Next, we will use repeated measures models to determine the association between change since baseline in the proposed mediators and current incontinence frequency, to show that changes in the mediator are associated with changes in the primary outcome, and to determine which of the proposed mediators independently predict change in incontinence frequency. Finally, we will examine the attenuation of the estimated effect of treatment on incontinence frequency after controlling for changes in the proposed mediators, as an estimate of the proportion of the treatment effect explained. Confidence intervals for proportion of the treatment effect explained will be computed.[75]

13.0 STUDY ORGANIZATION AND GOVERNANCE

PRIDE will be conducted at two Clinical Centers with extensive experience in recruitment of obese and overweight persons and in administering successful weight reduction programs (The Miriam Hospital/Brown Medical School and the University of Alabama). The trial will be coordinated at the Women's Health Clinical Research Center at the University of California, San Francisco. The Steering Committee will be the primary governing body of the study and will be comprised of the Principal Investigators from the Clinical Centers, a behavioral consultant from the University of Arkansas, the Principal Investigator and Co-Principal Investigator of the Coordinating Center and project scientists from NIDDK. In the development stage of PRIDE, the Steering Committee will direct refinement of the study design, completion of the protocol, and development of interventions, operations manual and data collection forms. As recruitment and enrollment begin, the Steering Committee will monitor study progress and quality, and resolve issues that arise during follow-up. Finally, the Steering Committee will review and approve proposals for ancillary studies, analyses, scientific presentations and manuscripts.

A Data and Safety Monitoring Board (DSMB) will be organized by the Project Office of the NIDDK. The DSMB will convene at the end of protocol development to review the protocol and develop guidelines for DSMB activities and stopping rules. They will meet 6 months after recruitment begins then approximately annually to review study progress, oversee participant safety, monitor data quality, and provide operational and technical advice to the Steering Committee and the NIDDK project officer. The DSMB will be comprised of five members with expertise in operational and biostatistical aspects of clinical trials, urinary incontinence and weight reduction. No member of the DSMB will participate in the study as an investigator or be involved in any way in the

conduct of the study.

CONFIDENTIAL

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PRIDE – Urodynamic Study Protocol

A substudy to the Program to Reduce Incontinence by Diet and Exercise (PRIDE): an NIDDK-sponsored, multi-center, randomized, controlled clinical trial comparing incontinence improvement between groups randomized to a weight reduction program or control in overweight or obese women with urinary incontinence

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SIGNATURE PAGE

FINAL PROTOCOL SIGNATURES:

	Name	Signature	Date
Investigator	Leslee Subak, MD		
Investigator	Holly Richter, MD		
Investigator	Deborah Myers, MD		
Principal Investigator	Deborah Grady, MD, MPH		

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1.0 BACKGROUND AND RATIONALE

Urinary incontinence is a prevalent health condition in women and has a significant impact on quality of life. Over 13 million Americans, including 25% of reproductive age women and up to 50% of postmenopausal women, are affected by stress (involuntary loss of urine with coughing, sneezing, straining, or exercise), urge (loss of urine associated with a strong need or urge to void) or mixed incontinence (episodes of both types).[1-3] Epidemiological studies suggest that obesity is a strong risk factor for urinary incontinence[4-7] and early observational[8, 9] and small cohort studies[10, 11]suggest that weight reduction may be an effective treatment for incontinence.

PRIDE — The **Program** to **Reduce Incontinence** by **Diet** and **Exercise** is a multicenter, randomized, clinical trial evaluating weight reduction as an innovative treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized to either a 6-month behavioral weight reduction program or control (instructional handouts and brief informational sessions on diet and exercise) and followed for 18 months. At baseline, all women will be given a pamphlet describing a self-administered behavioral treatment program for incontinence. **In a subgroup of 100 women, we will perform standardized pelvic floor evaluation and urodynamic studies at baseline and at 6 months to elucidate the mechanism by which weight loss improves incontinence.**

2.0 CLINICAL TRIAL OBJECTIVES

The primary aims of PRIDE are:

1. to determine whether randomization to a weight reduction program results in greater reductions in frequency of incontinence episodes at 6 months compared to control;
2. to identify women who are most likely to experience improved continence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed).

As a part of PRIDE we plan to:

1. conduct exploratory analyses to evaluate whether baseline urodynamic measures can identify women who are most likely to experience improved continence after weight reduction and;
2. investigate the mechanism by which weight loss improves continence by

examining the relationship of improvement in continence and changes in urodynamic measures.

To achieve these aims, the pelvic floor evaluation and urodynamic testing (UDS) will be performed on the first 50 volunteers at each site who agree and sign a separate informed consent. Standardized urodynamic testing will take place at baseline and again at the 6-month follow-up study visit.

3.0 STUDY DESIGN

100 overweight or obese women with urinary incontinence will undergo pelvic floor evaluation and urodynamic testing at baseline and at 6 months, following completion of either the 6-month weight reduction program or control. Women participating in PRIDE will be randomized in a 2-to-1 ratio to either of these treatment groups and it is expected that the randomization pattern will be reflected in the Urodynamic Substudy. (Please see the PRIDE Protocol for a complete description of the PRIDE study.)

3.1 Study Timeline

The first year of the study will include developing and refining the protocols, operations manual, forms, database, intervention materials and websites. Participant recruitment will begin in the first year and continue for approximately two years. The UDS evaluations will begin in year 2.

4.0 STUDY SITES

The study will be conducted at two clinical centers and three institutions: Miriam Hospital and Brown University, Providence, RI and the University of Alabama, Birmingham, AL. Data will be collected, managed and analyzed at the Women's Health Clinical Research Center, University of California at San Francisco, San Francisco, CA. A list of investigators is available at the PRIDE public website at: http://coordinatingcenter.ucsf.edu/pride/

5.0 STUDY POPULATIONS

5.1 Sample Size

Of the 330 volunteers for PRIDE, the first 100 women who agree to participate in the Urodynamic Study will be enrolled (approximately 50 at each of 2

clinical centers).

5.2 Inclusion and Exclusion Criteria

All participants must first meet the entry criteria for PRIDE and must sign an additional informed consent form for the Urodynamic Study. Because of weight limits for the urodynamic testing chairs and difficulty performing the evaluation in very obese women, participants with weight < 300 pounds are eligible for this sub-study.

6.0 ETHICS

6.1 Institutional Review Board

The study protocol, informed consent form, study questionnaires, educational and recruitment materials must be approved by the Institutional Review Board at each institution prior to the start of the study. Protocol amendments generated during the study must be approved by the IRBs prior to their implementation. Copies of all IRB approval letters will be sent to the Project Office at the NIDDK. Reports issued by the PRIDE Data and Safety Monitoring Board will be distributed to the investigators to be forwarded to their IRBs. Any serious adverse events that occur during the trial must be reported to each IRB.

6.2 Informed Consent Form

The UDS informed consent form will explain in lay language the goals of the substudy, the visits and procedures and the risks and benefits of participating. Any amendment to the protocol generated during the study that impacts participants will be reflected in a revised consent form that must be signed by the participant.

7.0 STUDY SCHEDULE AND PROCEDURES

7.1 Enrollment Procedures

7.1.1 Enrollment in the UDS substudy

Women enrolling in PRIDE will be randomly allocated in a 2-to-1 ratio

to either the weight reduction program or control condition. Prior to randomization, women will be asked to participate in the UDS substudy. A volunteer sample will be included. After the first 30 women are enrolled in the UDS substudy, we will evaluate the sample to assess the distribution of group assignment (weight loss or control condition), incontinence type and BMI. We will classify incontinence type as 1) stress only or mixed stress incontinence and 2) urge only or mixed urge incontinence. Our goal is to have a UDS substudy sample with approximately 67% women in the weight loss group, 50% with stress/mixed stress incontinence, and 50% with BMI < 35 kg/m^2. If there is >10% deviation from these goals, we will consider limiting enrollment in the UDS study to underrepresented intervention group, incontinence type or BMI category.

7.1.2 Ensuring Objective Assessments

Throughout the study every effort will be made to ensure objective and blinded assessments of outcomes. Staff who performs urodynamic studies will not be informed of the participant's treatment assignment. Care will be taken to avoid overtly identifying the treatment assignments on participant charts.

7.2 Study Visits

7.2.1 Recruitment

All women who are eligible and agree to participate in PRIDE will be offered the option of undergoing pelvic floor evaluation and urodynamic testing. The UDS substudy will be explained fully after the woman has completed her second screening visit. Those who agree to participate will be scheduled for a UDS visit in addition to the main study baseline visit.

7.2.2 Urodynamic Study Visits

At the baseline and at the 6 month urodynamic visits, a urogynecologist, or a designee under her supervision, will perform the pelvic floor evaluation using the Brink's score of pelvic muscle strength, Pelvic Organ Prolapse Quantification (POP-Q), and urethral hypermobility (Q-

tip test) and the urodynamic studies including passive uroflowmetry, filling cystometrogram, and cough stress test. Measurements, diagnoses, and terms will conform to the recommendations of the Committee on Standardization of Terminology of the International Continence Society and will use the same methods as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Urinary Incontinence Treatment Network studies.[12]

7.3 Urodynamic Study Procedures

Urinalysis A urine dipstick test for urinary tract infection will be done prior to the pelvic floor evaluation and UDS procedures. When there is suspicion for infection, the remainder of the urodynamic substudy evaluation will be postponed until the infection has been treated.

The Brink's Test assesses pelvic muscle strength by scoring perceived pressure on the examiner's finger, alteration of the vertical plane, and contraction time. [13] Using sterile gloves and lubricant jelly the examiner inserts one or two fingers into the participant's vagina and instructs the participant to squeeze the pelvic muscles. Any degree of flicker on the examiner's finger(s) is considered evidence of ability to contract the muscle. This test will assess three elements of the pubococcygeus muscle contraction: pressure, duration (using a stop watch that is accurate to the tenth of a second), and displacement.

The Pelvic Organ Prolapse Quantification (POP-Q) is a standardized description of the severity of pelvic organ prolapse with good inter- and intra-observer reliability for prolapse staging.[14-17] This procedure will be performed according to the guidelines established by the International Continence Society[18] and will be standardized as demonstrated in a videotape produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Exam"). Any prolapse will be noted and the maximum anterior-posterior length with maximum straining of the genital hiatus and perineal body will be measured and recorded. The six primary measuring points

are defined in the International Continence Society's standardization report and a detailed description is included in the PRIDE Operations Manual. Total vaginal length will be recorded.

The Q-Tip Test will be used to evaluate mobility of the urethra and bladder neck. A sterile, lubricated cotton or dacron swab (Q-Tip) is placed into the urethra until it lies just within the urethrovesical junction. The angle circumscribed by the distal end of the swab relative to the horizontal at rest and during maximum Valsalva effort is measured with a Robinson Pocket goniometer. Bladder neck hypermobility is defined as a resting angle >30^{o} or maximum straining angle >30^{o}.[19, 20]

The Cough Stress Test will be performed to determine the presence and degree of stress incontinence. Stress tests that are positive in the face of positive urine cultures will be repeated when the infection is resolved. After the participant voids, the bladder is emptied completely using a 12 French catheter. Then the bladder is retrograde gravity filled to 300 ml or maximum capacity, whichever is less and the catheter is removed. In the supine position, the participant is asked to Valsalva and cough. If no leaking is noted, the participant stands and is asked to Valsalva and cough. Participants with Stage III or IV anterior prolapse who have a negative cough stress test (do not leak) will have their prolapse reduced (instructions detailed in the PRIDE Operations Manual) and provocative maneuvers will be repeated. Stress incontinence is considered present when the participant demonstrates transurethral urine leakage with or immediately after increased intra-abdominal pressure (with Valsalva effort or coughing).

Non-Instrumented Uroflowmetry (NIF) is performed after the 300 cc cough stress test to measure maximum urine flow rate, mean flow rate, time to maximum flow, and voided volume. Any of the electronically derived methods of calculating the uroflowmetry values are acceptable. The uroflowmeter

should be calibrated in accordance with routine clinical site practice standards and the scale should be set to zero prior to the start of each participant's study. The participant will void into the uroflowmetry machine while in the sitting position on the Uroflow chair and a time-flow curve is recorded using a standard urodynamic recorder. Flow pattern is classified as either normal (continuous, smooth and arc shaped with high amplitude) or abnormal (doesn't meet these criteria). Post-void residual (PVR) volume will be measured with a catheter.

A Filling Cystometrogram (CMG)

will be performed to measure intravesical pressure (Pves), intra-abdominal pressure (Pabd), and subtracted detrusor pressure (Pdet). With the participant sitting in a 45 degree reclined position, the fluid-filled column-type tubing will be connected to a dual lumen 8 French catheter. An intravesical catheter will be placed and the bladder filled with room temperature saline or sterile water at a rate of 50 ml/min. A rectal catheter will be used to measure continuous intra-abdominal pressure. Pressures will be continuously recorded on a multichannel urodynamics recorder throughout the conduct of the CMG. Flow rate and volume will also be recorded continuously.

Bladder Sensation Parameters: Three bladder sensation parameters will be measured during filling cystometry. The participant is instructed to state when she has the sensation of 1) first desire to void, 2) strong desire to void, and 3) sensation of maximum cystometric capacity, using standardized definitions/descriptions.

To assess proper placement of catheters the participant is instructed to cough at various times during the cystometrogram and the examiner will then record the Valsalva Leak Point Pressure (VLPP) or absolute intravesical pressure during the Valsalva maneuver that produced leakage.

Procedures will differ slightly according to the presence or absence of Stage III or IV anterior prolapse and examiners

will follow instructions detailed in the PRIDE Operations Manual.

The following data points for the CMG will be calculated by the UCSF Coordinating Center for each participant prior to analyses:

- Bladder compliance *[Maximum Cystometric Capacity (MCC)/ (Pves at MCC - Pves at baseline)]*
- Mean of VLPP values obtained for unreduced and reduced measurements
  mean Pves = (Pves 1 + Pves 2 + Pves 3) / 3 or mean Pves = (Pves 1 + Pves 2) / 2
- VLPPs from different baselines with and without reduction *(mean Pves - Pves at baseline)*

8.0 Quality Control Standards

The POP-Q test is performed according to the guidelines established by the International Continence Society[18]. The Brink's and Q-Tip tests will be performed by accepted guidelines and following techniques instituted by the Urinary Incontinence Treatment Network (UITN) UDS Working Group.

Several testing standards have been established by the UITN UDS Working Group in an effort to minimize variability of UDS completion and interpretation across Testers / Observers. The PRIDE UDS standards follow recommendations of the ICS Standardization Committee of Good Urodynamic Practice recently published by Schafer and others.[21] Both sites will use water perfusion catheters with baseline zeroing to atmospheric pressure. They will provide to the Coordinating Center copies or duplicate originals of tracings, graphs and output from the urodynamic studies as well as a clinical interpretation of the UDS in narrative form completed by a PRIDE physician investigator.

Standards for Signals (AKA: tracings, graphs, recorder output)

An original printout of the UDS signals (tracings) should be retained in the participant's research record and another printout (preferably another original) should be mailed to the central repository at the UCSF Coordinating Center (CC) along with all other required source documentation. (Participant names should be masked before transmission. Unique code numbers will be used to identify participant records.) UDS

data will be transmitted to the repository electronically following data management and data transmission procedures described elsewhere.

A) **Graph scaling**: the scaling of the signals will be standardized across centers and kept unchanged as much as possible. Urodynamic quality control is dependent on the tester's ability to recognize patterns, and the recognition of patterns is greatly improved by standard scaling of the signals.

b) **Labeling**: The signals of each respective study will be **clearly labeled;** i.e. non-instrumented uroflowmetry (NIF) vs. CMG, to simplify a central review. The CC will provide a labeling system for sites.

c) **Annotation:** The signals will be annotated in accordance with the required PRIDE data points.

Interpretation of the UDS and completing the PRIDE Data Form

A PRIDE Physician Investigator must verify, validate and confirm that the UDS was completed in accordance with sound clinical practice and in compliance with the PRIDE UDS protocol. To minimize invalid and missing data, a PRIDE Physician Investigator will review the UDS signals prior to removal of the catheters. If valid UDS data points cannot be abstracted from the signals, studies should be repeated whenever clinically feasible.

UDS data points that are artifactual, not interpretable, or deemed invalid by the PRIDE Physician Investigator will not be recorded on the PRIDE Data Form. If studies cannot be repeated, these data fields will be filled with a special missing values code to indicate the data are deemed invalid.

9.0 Serious Adverse Events

The risk of urodynamics testing is minimal. Serious adverse events as defined by the US Food and Drug Administration (death, a life-threatening event, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability or incapacity) will be routinely ascertained in this trial. Important medical events may be considered serious adverse experiences by the clinical site investigator if the event might jeopardize the participant or might require medical or surgical intervention to prevent one of the outcomes defined as serious.

Safety-related events will be reported in a timely fashion as required by the Data and Safety Monitoring Board and the IRB.

10.0 Data Management

10.1 Data Collection

Data forms will be filled out at the clinical sites after each of the urodynamic study visits and sent to the Coordinating Center via standard fax machines. Detailed instructions will be provided in the PRIDE Operations Manual.

10.2 Data Processing

All study data are subject to a set of daily error-checking programs. This routine includes checks for completeness, data consistency, and invalid ranges. The results are posted to the study website where clinical site personnel check daily to confirm that the CC has received all of the faxed forms and to address any queries.

A password-protected www site will be the study's data collection hub. Computers at the clinical centers will access a secure and private UCSF CC www server that provides continually updated data summary reports. Staff at clinical centers will edit data forms on the website. Access to these pages will be restricted to authorized personnel.

10.3 Data Confidentiality

Participant information is transmitted to the PRIDE Coordinating Center on data forms on which the participant is identified by a code number only. Participant names are confidential and only the clinical site staff will retain files that identify participants by name. Participant names on raw data that will be transmitted to the Coordinating Center (such as UDS recordings) must be blacked out and the participant's code number must be written on the recording instead.

11.0 Statistical Analysis

This will be an exploratory analysis of potential mechanisms for improvement in incontinence with weight loss. A series of closely related mixed linear models will be

used to assess mechanisms by which the weight loss intervention potentially affects measured incontinence frequency as well as related quality of life measures. We will first assess modification of the effects of treatment by baseline urodynamic measurements of leak point and intravesical pressures, to determine if the effectiveness of the weight loss intervention varies by these parameters. To maximize efficiency, effect modification will be assessed as a continuous interaction between treatment assignment and the urodynamic measures. We will then examine the overall effects of assignment to the weight loss arm on the urodynamic measures as well as weight loss, to show the effect of the intervention on the proposed mediators. Next, we will use repeated measures models to determine the association between change since baseline in the proposed mediators and current incontinence frequency, to show that changes in the mediator are associated with changes in the primary outcome, and to determine which of the proposed mediators independently predict change in incontinence frequency. Finally, we will examine the attenuation of the estimated effect of treatment on incontinence frequency after controlling for changes in the proposed mediators, as an estimate of the proportion of the treatment effect explained. Confidence intervals for proportion of the treatment effect explained will be computed.[22]

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PRIDE - Study Protocol

Program to Reduce Incontinence by Diet and Exercise (PRIDE):

an NIDDK-sponsored, multi-center, randomized, controlled clinical trial comparing incontinence improvement between groups randomized to a weight reduction program or control in overweight or obese women with urinary incontinence

AMENDMENT #5 to: PRIDE - Study Protocol
Date of Amendment: May 16, 2007

Summary of Changes in Amendment #5:

The application for funding for PRIDE II, an extended follow-up to PRIDE, was denied by the NIDDK. All participants have been notified. All references to extended follow-up have been deleted from the protocol. Specifically, Section 8.3.6 on page 20 has been deleted.

Summary of Changes in Amendment #4:

Although the PRIDE results are not yet available, the investigators would like to follow all PRIDE participants for another 18 months through an extension to the protocol to be referred to as **PRIDE II.** There will be no diet, exercise or educational classes provided during PRIDE II and the two study visits will be the same for all participants regardless of their previous randomization groups. **Any woman who was randomized to the PRIDE study will be eligible to participate in PRIDE II.**

Section 8.3.6: Extended Follow-up Visits

New Text in italics: *At the final PRIDE visit (or by mail/phone for those women who have already completed PRIDE), each participant will be invited to continue her participation for an additional 18 months. This extended observational follow-up, referred to as* ***PRIDE II,*** *includes no interventions, and there will be no restrictions on treatments for weight or urinary incontinence that participants may choose.*

Participants will be asked to sign a new consent agreeing to take part in ***PRIDE II****, which will include two follow-up visits 24 months and 36 months from their original randomization date. At the two follow-up visits participants will provide a health status update, have their weight and waist measured, complete a 7-day voiding diary and fill out questionnaires related to Quality of Life that were also completed during PRIDE at months 6, 12 and 18. Participants will be given an honorarium of $100 at the 24 month and $150 at the 36-month visit. If participants choose to take part in* ***PRIDE II****, they will have no restrictions on their choices of diet, exercise or treatment of urinary incontinence.*

Summary of Changes in Amendment #3:

1. The body mass index (BMI) entry criterion for PRIDE has been changed from a range of 25 – 45kg/m^2 to a range of 25 to 50 kg/m$^{2.}$

Section 6.2: Inclusion criteria (3)

New Text: body mass index 25 to 50 kg/m^2

Summary of Changes in Amendment #2

1. Inclusion criterion #4 has been corrected. Eligibility is determined by the number of incontinence episodes recorded on the screening diary, rather than on the diary completed at baseline.

Section 6.2: Inclusion criteria (4)

New text in italics: "current urinary incontinence symptoms for ≥ 3 months by self-report and record ≥ 10 incontinent episodes per week *during screening* on a 7-day urinary diary "

2. The 3-month follow-up visit has been eliminated in order to reduce the burden on participants and staff. The elimination of a weight measurement and a voiding diary at this time point will not affect the outcome data. A short participant satisfaction questionnaire will be administered three months after randomization to all participants at either a Lifestyle Intervention or a Structured Education session.

Section 8.1: Summary of Study Visits

The weight measurement and voiding diary are removed from the schedule. The UI Satisfaction questionnaire is added at 3 months.

Section 8.3.5: Follow-up Visits

New text in italics: "At 3 months participants *will complete a participant satisfaction questionnaire during one of the Lifestyle Intervention or Structured Education sessions."*

3. Text has been added to clarify the randomization procedures for the intervention and maintenance phases.

Section 8.2.2: Randomization to Motivation-based or Skill-based Weight Maintenance

New Text in italics: "Blocked randomization within each center will be done to ensure that *Group A is not always assigned to the same maintenance intervention and that* the number of participants is equally distributed between the maintenance strategies."

Section 8.3.4: Randomization/Baseline Visit

New Text in italics: **"**The list of inclusion and exclusion criteria will be reviewed and participant eligibility will be confirmed. *Participants are then randomized individually during visits that are clustered closely together. Participants open a sequentially numbered randomization envelope that contains their assignment to one of three groups identified by a number identifying the recruitment wave) and a letter identifying the group, for example, treatment group 1A or 1B, or control group 1C. Treatment groups A and B will be re-randomized at month 6 for the maintenance phase, preserving the original group structure."*

Summary of Changes in Amendment #1:

1. The education schedule for the control group program sessions has been changed from weeks 2, 4, 6 and 8 to months 1, 2, 3 and 4.

Section 9.2 Education for the Control Condition

New Text in italics: "women randomized to the control condition (entitled the "Structured Education Program"), will be invited to participate in hour long group educational sessions at *months 1, 2, 3, and 4"*

2. Participants may sign informed consent at the Orientation Visit and the urinalysis dipstick may be repeated at SV2 if necessary.

Section 8.3.2: Screening Visits

New Text in italics: **"**Eligible respondents may be invited to attend a group Orientation Visit where the purpose, study schedule and informed consent document will be described briefly, questions answered, and general eligibility and interest level assessed. *Participants may sign informed consent after the orientation.* Interested participants will be invited back for a Screening Visit 1 (SV1) where the study will be explained in detail, informed consent will be obtained *(if not at OV)*, and confirmatory measures of eligibility will be performed (weight, height, blood pressure, urine analysis). ……. (Height,

weight and blood pressure should be performed at this visit if they were not done at SV1.) Repeat blood pressure *and urinalysis* measurements are allowed at this visit if the participant failed the eligibility criterion at SV1."

3. "Baseline Visit" has been changed to "Randomization Visit". The protocol and informed consent have been altered to reflect this change.

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1.0 Brief Summary

PRIDE — The Program to Reduce Incontinence by Diet and Exercise is a multicenter, randomized, clinical trial evaluating weight reduction as a treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized in a 2-to-1 ratio to either a 6-month weight loss program (lifestyle and behavior change) or control group (instructional handouts and brief informational sessions on diet and exercise) and followed for 18 months. At randomization, all women will be given a pamphlet describing a self-administered behavioral treatment program for incontinence. At 6 months, a second randomization will be done among women who complete the weight reduction program to test whether a motivation-based weight maintenance program results in superior long-term weight loss at 18 months compared to a skill-based maintenance program. In a subgroup of 100 women, we will perform standardized urodynamic studies to explore the mechanism by which weight loss improves incontinence.

2.0 Background and Rationale

Urinary incontinence is a prevalent health condition in women and has a significant impact on quality of life. Over 13 million Americans, including 25% of reproductive age women and up to 50% of postmenopausal women, are affected by stress (involuntary loss of urine with coughing, sneezing, straining, or exercise), urge (loss of urine associated with a strong need or urge to void) or mixed incontinence (episodes of both types).[1-3] While incontinence does not lead to death,[4] it is associated with a profound adverse effect on quality of life,[2, 5-7] a 20-30% increased risk of falls and fractures,[8] a three-fold increased risk of nursing home admissions,[9] and over $16 billion in annual direct costs.[10]

Current incontinence treatment is not satisfactory. The first line of treatment typically used for both stress and urge incontinence is bladder training, toileting assistance, and/or pelvic muscle rehabilitation.[11-13] These behavioral approaches are only modestly effective, and in many cases, a second line of therapy is needed. Pharmacological therapy, primarily with anticholinergic medications, is frequently the second line of therapy for urge incontinence and results in a 15-60% reduction in weekly incontinent episodes. However, anticholinergic side effects are common and the medications must be taken chronically.[1, 14-16] Newer medications and reformulations of older drugs provide better tolerability, but long-term compliance remains low.[17, 18] Surgery is another highly effective second

line treatment, but incontinence tends to recur over time and surgery is associated with discomfort, a prolonged recovery period, and operative complications, particularly in obese women.[19, 20]

Obesity is a strong risk factor for incontinence. Among older women with incontinence, 65 to 75% are overweight or obese. Moreover, epidemiological studies suggest that obesity is a strong risk factor for urinary incontinence.[21-24] Over 50% of American women are overweight (body mass index (BMI) 25 to 30 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2), and the prevalence of obesity is dramatically increasing.[25-29] In addition to the impact urinary incontinence has on quality of life and morbidity, obesity itself contributes to over 300,000 deaths per year. It is associated with increased risk for heart disease, hypertension, diabetes, cancer, arthritis, respiratory disease and depression [30, 31] and has direct and indirect costs of over $100 billion per year.[32] Thus, women who are both overweight and incontinent are at high risk for negative health outcomes and impaired quality of life.

Weight reduction may be an effective treatment for incontinence. In observational studies, morbidly obese women (>45 kg above ideal weight) with incontinence who had dramatic weight loss after bariatric surgery (45-50 kg) had significant improvement in urinary incontinence.[33, 34] Similarly, positive results were obtained in a small prospective cohort study with overweight and obese incontinent women enrolled in weight reduction programs.[35] Six of six women achieving a weight loss of $\geq$5% had at least a 50% reduction in incontinence frequency compared to one of four women with <5% weight loss ($p = 0.03$). A 3-month randomized trial of a very low calorie liquid diet program compared to no intervention among 42 overweight and obese women with incontinence resulted in an average weight loss of 14 kg in the intervention group. The frequency of incontinence episodes was reduced significantly among women assigned to the weight loss group.[36] Thus, even modest weight reduction may be a clinically feasible treatment option for incontinence and may, in addition, improve control of hypertension, hyperglycemia, hyperlipidemia, reduce the risk of developing type 2 diabetes,[37] and produce marked improvements in mood and quality of life.[38]

The importance of weight maintenance. If the hypothesis that weight reduction improves incontinence is correct, then maintaining improvement in incontinence will depend on maintaining weight loss.

Standard approaches to weight loss maintenance have focused on helping participants refine their weight reduction skills.[39] Advances that have improved the efficacy of weight loss maintenance, and that have been incorporated into standard maintenance programs, include increased physical activity,[40] ongoing contact with the therapist and weight loss group,[41, 42] and increased attention to problem solving skills.[43] Despite these additions, weight regain still occurs and by 18 months most programs obtain average weight losses of only 5-6 kg.[44] Developing a more effective long-term weight loss intervention is the top research priority in the behavioral treatment of obesity[45] and is clearly needed if weight loss is to be a lasting treatment for incontinence.

3.0 Clinical Trial Objectives

3.1 Primary aims of PRIDE are to:

1. determine whether randomization to a weight reduction program results in greater reductions in frequency of incontinence episodes at 6 months compared to a control condition;
2. determine if randomization to a motivation-based weight maintenance program results in less weight regain compared to a skill-based maintenance program from the end of the weight reduction program (6 months) to the end of the weight maintenance program (18 months);

3.2 Secondary aims are to:

3. identify women who are most likely to experience improved continence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed).
4. determine if randomization to a weight reduction program results in greater improvement in continence from baseline to 18 months compared to a control condition and whether the motivation-based weight maintenance program results in greater improvement in continence from baseline to 18 months than the skill-based weight maintenance program or control condition.
5. randomization to a weight reduction program results in greater improvement in quality of life from baseline to 6 and to 18 months compared to a control condition.

3.3 Tertiary aims in a volunteer subset of 100 participants are to:

6. evaluate whether urodynamic measurements can identify women who are most likely to experience improved continence after weight reduction
7. investigate the mechanism by which weight loss improves continence

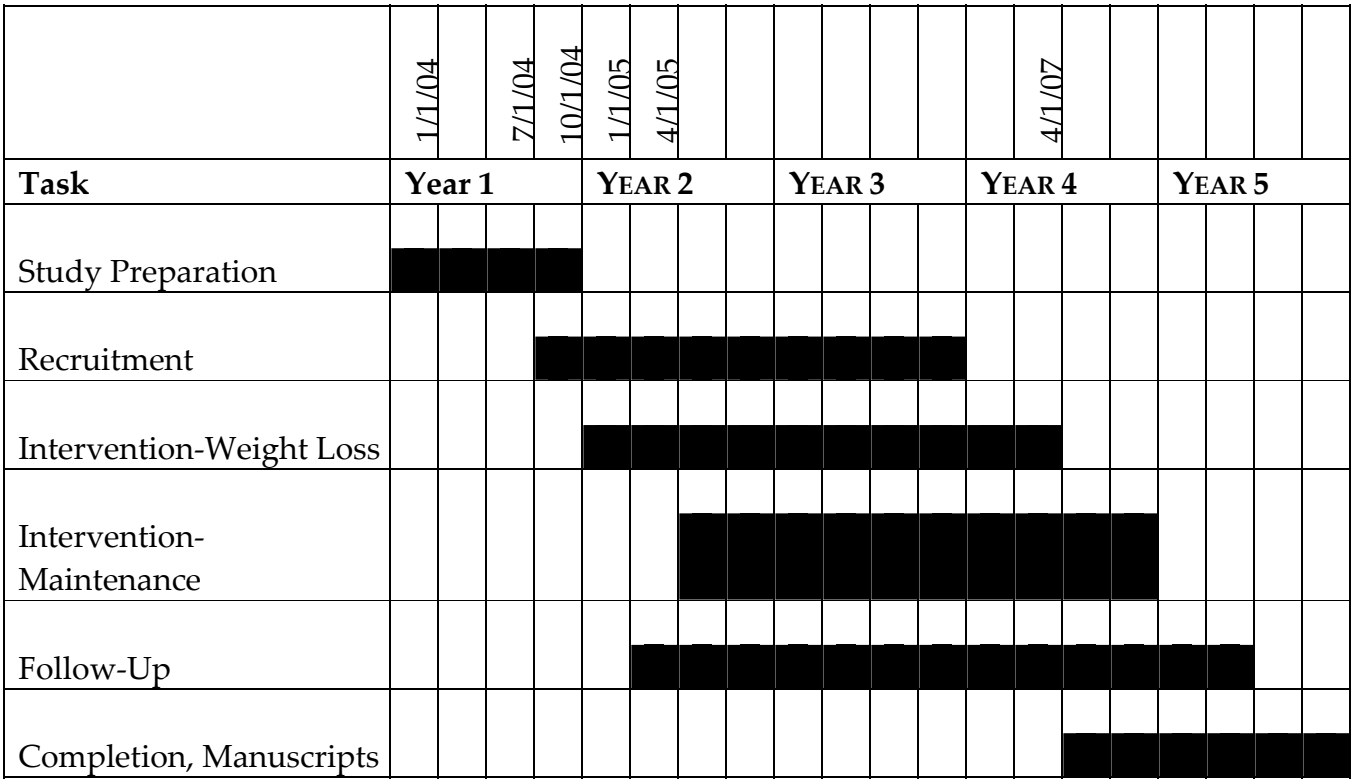
4.0 Study Design

330 overweight or obese women with urinary incontinence will be randomized in a 2-to-1 ratio to either a 6-month lifestyle and behavior change weight reduction program or to a control condition (no weight reduction intervention) and followed for 18 months. At randomization, all women will be given a pamphlet describing a self-administered behavioral treatment program for incontinence (instructional booklet with voiding diaries, bladder training and pelvic muscle exercises). After completing the 6-month weight reduction program, women in this treatment arm will be randomized to either a motivation-based or a skill-based weight maintenance program. In a volunteer subgroup of 100 women, urodynamic studies will be performed at baseline and 6 months.

4.1 Study Timeline

The first 9 months of the study will include developing and refining the protocol, operations manual, forms, database, intervention materials and website. Participant recruitment will begin in the first year and continue through the end of the third year. Enrollment and intervention will begin in year 2 and follow-up will be completed in mid-year 5. The final year of the study will include completing data collection and editing, data analyses, scientific presentations and manuscript preparation.

Project Plan:



5.0 Study Sites

The study will be conducted at two clinical centers: Miriam Hospital, Brown University, Providence, RI and the University of Alabama, Birmingham, AL. Data will be collected, managed and analyzed at the Women's Health Clinical Research Center, University of California at San Francisco, San Francisco, CA.

A list of investigators is available at the PRIDE public website at: http://coordinatingcenter.ucsf.edu/pride/

6.0 Study Population

6.1 Sample Size

A total of 330 overweight and obese women with urinary incontinence will be recruited (165 at each of 2 clinical centers).

6.2 Inclusion Criteria

1. women aged ≥ 30 years
2. not institutionalized
3. body mass index 25 to 50 kg/m^2
4. current urinary incontinence symptoms for ≥ 3 months by self-report and record ≥ 10 incontinent episodes per week during screening on a 7-day urinary diary
5. able to complete a behavioral run-in consisting of self-monitoring of food and activity
6. report having a primary health care provider
7. able to understand and sign informed consent and complete baseline questionnaires
8. able to walk 2 blocks without stopping and without a cane or walker
9. agree not to initiate new treatment for incontinence or weight reduction, including behavioral, pharmacological or surgical therapies, for the duration of the study

Age and body mass index ranges were selected to identify a population most likely to respond to the intervention and safely able to participate in a behavioral weight loss program.

6.3 Exclusion Criteria

1. current use, or use within the previous month*, of medical therapy for incontinence or weight loss
2. pregnant or gave birth in the previous 6 months
3. urinary tract infection (dipstick urinalysis positive for leukocyte estrace, nitrites or blood) or report having ≥ 4 urinary tract infections in the preceding year
4. incontinence of neurologic or functional origin (by history)
5. report prior anti-incontinence or urethral surgery, pelvic cancer or pelvic irradiation
6. report significant medical conditions of the genitourinary tract (genitourinary fistula, interstitial cystitis, symptomatic pelvic organ prolapse)
7. report a medical condition that would affect the safety and/or efficacy of a weight management program involving diet and physical activity, including type 2 diabetes requiring medical therapy that may cause hypoglycemia, chronic steroid use or uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure > 100 mm Hg); women with a history of coronary heart disease may participate with written approval from their primary care physician
8. engaged in an active weight loss program and/or experienced a weight reduction of 10 lbs or more in the past 3 months
9. report conditions that, in the judgment of the clinical center Principal Investigator, render potential participants unlikely to follow the protocol for 18 months, including illness likely to be terminal within 2 years, plans to move, substance abuse, significant psychiatric problems, or dementia
10. participating in another research study that involves investigational drugs or can potentially confound the results of PRIDE

* Potential participants may be re-screened one month after stopping medical therapy for incontinence or obesity. Prior medical therapy for incontinence or obesity will not affect eligibility but participants will be asked not to initiate any

treatment for incontinence or obesity during the study period except as directed by the study protocol.

7.0 Ethics

7.1 Institutional Review Board

The study protocol, informed consent form, study questionnaires, educational and recruitment materials must be approved by the Institutional Review Board at each site and the coordinating center prior to the start of the study. Protocol amendments generated during the study must be approved by the IRBs prior to their implementation. Copies of all IRB approval letters will be sent to the Project Office at the NIDDK. Reports issued by the PRIDE Data and Safety Monitoring Board will be distributed to the investigators to be forwarded to their IRBs. Any serious adverse events that occur during the trial must be reported to each IRB.

7.2 Informed consent form

Before individuals may participate in any screening procedures, informed consent for all phases of the trial must be obtained. The consent form will explain in lay language the goals of the study, the visits and procedures and the risks and benefits of participating. A separate protocol and consent form will be required for the 100 participants who volunteer for the urodynamic investigation. Any amendment to the protocol generated during the study that impacts participants will be reflected in a revised consent form that must be signed again by the participant.

8.0 Study Schedule and Procedures

8.1 Summary of Study Visits

Measures	OV	SV1	SV2	UDS	RV	6 mo	12 mo	18 mo
Describe study requirements	X							
Obtain Informed Consent	Y	Y						
Obtain physician consent		Y	Y					
7-day voiding diary		Y	Y		X	X	X	X
Dipstick urine analysis		Y	Y	X				
Height & Weight for BMI		Y	Y					
Weight					X	X	X	X
Waist Circumference					X	X	X	X
Blood Pressure		Y	Y			X	X	X
Demographic factors		Y	Y					
Medical/surgical/gynecological/incontinence history		Y	Y					
Training for diet & exercise diary, and completing questionnaires		Y	Y					
24 hour Pad Test			X			X	X	X
Incontinence questionnaire			X			X	X	X
Sexual function questionnaire			X			X	X	X
Bowel function questionnaire			X			X	X	X
Food Frequency Questionnaire			X			X	X	X
Motivation Questionnaires			X			X	X	X
Paffenbarger Activity Questionnaire			X			X	X	X
Sleep questionnaire			X			X	X	X
Incontinence Impact Questionnaire			X			X	X	X
Urogenital Distress Inventory			X			X	X	X
Short form 36			X			X	X	X
UI - Satisfaction measures						X	X	X
Beck Depression Inventory			X			X	X	X
Urodynamic assessment*				X		X		

Brinks Score, Pelvic, Q-tip & POP-Q exam*				X		X		

*Note: These measures are completed only on the first 50 women at each site to volunteer for more extensive testing.
Y = measurement can be completed at either screening visit
TS = Telephone Screen; OV=Orientation Visit; SV=Screening Visit; RV=Randomization Visit; UDS=UroDynamic Study Visit

8.2 Randomization Procedures

8.2.1 Randomization to Weight Loss or Control. Women will be randomly allocated in a 2-to-1 ratio to either the weight reduction program or control condition. Randomization will be stratified by clinical center. Blocked randomization within each of the centers will then be performed to ensure that the number of participants in the two treatment groups is close to our goal of an exact 2 to 1 ratio. Since the intervention is not strictly blinded, block size will vary randomly from 3 to 6 in a schedule that is not known to investigators. In addition, to assure an even distribution of treatment groups, a separate set of randomization envelopes will be prepared, as described above, for women who choose to have the urodynamic assessment. Thus, the randomization will be stratified both by center and whether or not the participant volunteers for the urodynamic assessment.

Using computer algorithms for a 2 to 1 randomization, Coordinating Center staff will prepare two sets of sealed, opaque envelopes for each clinical center, color coded for urodynamic assessment or no urodynamic assessment. On the outside, the envelopes will be numbered consecutively with the randomization sequence number; on the inside the envelopes will contain study group assignment. When eligibility has been confirmed by completion of the eligibility checklist, clinical center staff will enter the date, participant's name, and study ID (assigned at the screening visit) consecutively in a randomization log, select the next numbered randomization envelope from the appropriate color-coded series, enter the randomization sequence number listed on the outside of the envelope, then open the envelope and enter the study group assignment contained inside the envelope on the randomization log. All opened and unopened envelopes will be retained at the clinical center for review during study site visits and at the end of the trial. Randomization dates and times should follow the order of the randomization sequence numbers, providing a check on validity. Screening data

will be retained by study ID for women not randomized, facilitating review of the recruitment process.
Participants will be randomized in "waves" of about 30 – 40 at a time to accommodate the formation of intervention or control groups. Eligibility is determined during screening visits.

8.2.2 Randomization to Motivation-based or Skill-based Weight Maintenance. After 6 months of weight reduction intervention, women in the weight reduction group will be cluster randomized by weight reduction group, with equal probability of the group being assigned to either motivation-based or skill-based weight maintenance strategies. Clustered randomization will introduce some complexity in the analyses. However, we believe this problem is outweighed by the support and enthusiasm that typically develops among the 10-20 women in each weight reduction counseling group who have been working together to lose weight for 6 months. Blocked randomization within each center will be done to ensure that the number of participants is equally distributed between the maintenance strategies. This is done to assure that Group A is not always assigned to the same maintenance intervention. Since the intervention cannot be easily blinded, block size will vary randomly from 2 to 4 groups in a schedule that is not known to investigators. For each clinical center, a set of opaque envelopes containing treatment assignment for each weight reduction group will be prepared by the Coordinating Center. Each weight reduction group will be numbered during the weight reduction intervention. At the end of the weight reduction intervention, the number of each group will be entered on a randomization log, and the next consecutive envelope will be opened to determine treatment assignment. This treatment assignment will be entered in the randomization log for each member of the weight loss group.

8.3 Study Visits

8.3.1 Recruitment Phase. Women will be recruited by (1) direct, community-based efforts using large media (newspaper notices, television ads, etc) and small media (brochures in local businesses, talks to local community, notices in churches, salons etc); (2) seeking referrals from physician's offices (specifically in gynecology, primary care, and geriatric medicine) and (3) purchasing targeted mailing lists. Every effort will be made to assure significant representation of minority women by working with key community leaders, building trust and gaining support, as well as providing community education about the nature of the health problems addressed within the project

(incontinence and obesity). Transportation and parking costs may be reimbursed and participants will be provided a stipend for attending assessment visits. The individual clinical centers will be responsible for recruiting the required number of subjects and the Coordinating Center will provide centrally developed recruitment materials. The Coordinating Center will monitor recruitment at each clinical center on a real-time basis, lead periodic conference calls about recruitment and retention, and provide regular reports to the Steering Committee, Data and Safety Monitoring Board and the NIDDK.

8.3.2 Screening Visits. Women who respond to study advertisements will be called on the telephone, provided a general overview of the study and, if interested, will complete a brief survey to determine initial eligibility. Eligible respondents may be invited to attend a group Orientation Visit where the purpose, study schedule and informed consent document will be described briefly, questions answered, and general eligibility and interest level assessed. Participants may sign informed consent after the orientation. Interested participants will be invited back for a Screening Visit 1 (SV1) where the study will be explained in detail, informed consent will be obtained, and confirmatory measures of eligibility will be performed (weight, height, blood pressure, urine analysis). Participants will be trained to keep 7-day diaries of food intake, physical activity, and voiding and will be given baseline questionnaires assessing incontinence severity and distress, dietary intake and physical activity patterns. These will be completed at home and returned at Screening Visit 2 (SV2). After a 1-2 week period has elapsed, participants will return to the clinical center for SV2, where the diaries and questionnaires will be reviewed for completeness and eligibility. (Height, weight and blood pressure should be performed at this visit if they were not done at SV1.) Repeat blood pressure and urinalysis measurements are allowed at this visit if the participant failed the eligibility criterion at SV1. To be eligible, participants must record having had at least 10 episodes of incontinence during the prior week on the voiding diary. Eligible participants will be given a new 7-day voiding diary, the 24-hour pad test kit, and the self-administered health assessment and motivation questionnaires to complete at home. The pads will be mailed back to the clinic and the questionnaires and diaries should be returned at the Randomization Visit (RV). Urodynamic testing procedures will be discussed.

8.3.3 Urodynamic Study Visit. To explore mechanisms by which weight loss may result in improved continence, 50 volunteers at each site will be scheduled for a Urodynamic Study visit (UDS) prior to randomization and at

Month 6. To ensure equal distribution of participants across treatment groups the 100 volunteers will be randomized separately as described in Section 8.2.1. At this visit, Pelvic Organ Prolapse Quantification (POP-Q), urethral hypermobility (Q-tip test), Brink's score of pelvic muscle strength and urodynamic studies including passive uroflowmetry, filling cystometrogram, and cough stress test studies will be performed. Measurements, diagnoses, and terms will conform to the recommendations of the Committee on Standardization of Terminology of the International Continence Society and will use the same methods as the NIDDK-funded Urinary Incontinence Treatment Network.[46] The POP-Q is a standardized description of the severity of pelvic organ prolapse with good inter- and intra-observer reliability for prolapse staging.[47-50] Mobility of the urethra and bladder neck will be evaluated using the Q-tip test, with bladder neck hypermobility defined as a resting angle >30^{o} or maximum straining angle >30^{o}.[51, 52] The Brink's test assesses pelvic muscle strength by scoring perceived pressure on the examiner's finger, alteration of the vertical plane, and contraction time. [53] The urodynamic measures have been demonstrated to be reproducible, to correlate with each other, and to correlate with clinical measures of incontinence severity.[54-57] These measures will be used to identify women who are more likely to have improvement in continence due to weight loss and to explore mechanisms by which weight loss might improve continence. We will perform these tests in a subset of participants because these tests are expensive and invasive, and our hypotheses regarding how weight loss may affect continence are exploratory.

8.3.4 Randomization Visit. At the randomization visit, weight and waist circumference will be measured and the second 7-day voiding diary will be reviewed. The following self-administered questionnaires will be reviewed for completeness: Food Frequency Questionnaire, motivation questionnaires, Paffenbarger Activity Questionnaire, Incontinence Impact Questionnaire, Urogenital Distress Inventory, Short Form 36, Beck Depression Inventory and Health Satisfaction rating. All participants will be given the urinary incontinence self-administered behavioral training booklet. Pads distributed at SV2 will be weighed as soon as they are received at the site. The list of inclusion and exclusion criteria will be reviewed and participant eligibility will be confirmed. *Participants are then randomized individually during visits that are clustered closely together. Participants open a sequentially numbered randomization envelope that contains their assignment to one of three groups identified by a number identifying the recruitment wave) and a letter identifying the group, for example, treatment group 1A or*

1B, or control group 1C. Treatment groups A and B will be re-randomized at month 6 for the maintenance phase, preserving the original group structure.

8.3.5 Follow-up Visits. At 3 months participants will complete a participant satisfaction questionnaire during one of the Lifestyle Intervention or Structured Education sessions. At 6, 12 and 18 months, participants will be seen at the clinical centers to repeat weight, waist circumference, pad test, self-administered health assessment questionnaires and the diet, exercise and voiding diaries. The 7-day voiding diary, pad test kit, diet and exercise diaries and questionnaires will be mailed to participants 3 weeks before the follow-up visits. Participants will complete these measures at home and return them at their visit to be reviewed by study staff. Participants will be asked to bring to the visit all prescription and non-prescription medications that they are currently taking and these will be recorded.

8.4 Study Measures

8.4.1. 7-day voiding diary. Voiding diaries serve as the primary outcome instrument to measure change in symptoms of urinary incontinence. The diary includes frequency of micturitions (diurnal and nocturnal) and incontinence episodes classified by clinical type (urge, stress, other) along with time of occurrence. Simple written instructions and a sample of a completed diary will be given to participants. Study staff will review instructions for completion of the diary with the participant to ensure proper understanding. All participants will complete voiding diaries at each assessment point and diaries will be given or mailed to the participant prior to the visit. Participants will be asked to bring the completed diary with them to the visit. The clinic staff will review diary entries for completeness, summarize the information and fax the summary data into the database. Copies of the diaries will be sent to the Coordinating Center where staff will perform the same summarization, entering the summary data into the database as a quality control check of the primary outcome variable.

8.4.2. 24 hour pad test. Pad testing will be used to quantify the amount of urine lost involuntarily and will reflect everyday incontinence. This standardized test[46] correlates well with incontinence symptoms, and has good reproducibility. The 24-hour pad test includes simple written instructions, pads, plastic storage bags and addressed, stamped envelope to return the pads to the clinical site. Study staff will review instructions for completion of the test with the participant to ensure that she understands how to properly complete the test.

Every effort will be made by study staff to encourage participants to fully complete the test by collecting all pads. All participants will complete 24-hour pad tests at each assessment point. A secondary outcome of this study is the change from baseline in pad weight for a 24-hour pad collection at the 6, 12 and 18-month follow up.

8.4.3. Incontinence questionnaire. The incontinence questionnaire is a self-report measure of incontinence severity. It includes the 2 Incontinence Questions (2IQ), American Urological Association Symptom Index (AUA Symptom Index), Sandvik Severity Index, and Incontinence Expense Questionnaire. The 2IQ is a short questionnaire to diagnose the type of urinary incontinence in women. It is currently being studied in a multi-site study to compare the accuracy of the 2 -IQ compared to a standard extended evaluation for diagnosis of incontinence type (Diagnostic Aspects of Incontinence Study; Coordinating Center PI: D. Grady). We have added a third question to assess bothersomeness of each type of incontinence. The AUA Symptom Index and the Sandvik Severity Index are validated instruments to assess lower urinary tract and incontinence symptoms, respectively. For the Incontinence Expense Questionnaire, participants record resources used in an average week specifically for incontinence (pads, protection, laundry, dry cleaning). A generalizable cost for the resources is then estimated by multiplying resources used by national resource cost estimates.

8.4.4. Sexual function questionnaire. The sexual function questionnaire is a self-report survey of sexual activity, satisfaction with sexual activity and four sexual function domains (interest, ability to relax, arousal and orgasm).

8.4.5. Bowel habits questionnaire. The Bowel Habits Questionnaire is a self-report survey to assess bowel function and habits, including frequency, consistency, straining with bowel movements, constipation, fecal and flatal incontinence. The questionnaire was developed from often-used instruments, including the ROME II criteria, Gastrointestinal Quality of Life Index, and **scoring system for the assessment of bowel and lower urinary tract symptoms in women.** The Bowel habits Questionnaire in PRIDE underwent extensive pretesting and is currently being validated in the Reproductive Risks for Incontinence Study at Kaiser (RRISK).

8.4.6. Weight, height and body mass index Weight will be recorded in kilograms using a calibrated scale. Participants will be measured in light clothing

(without shoes) to the nearest 0.5 kg. Standing height, which is measured at the screening visit only, will be measured in millimeters with a wall-mounted Harpenden stadiometer. Body mass index will be calculated from body weight and height as weight in kg divided by the square of height in meters. Body mass index will be used to verify study eligibility.

8.4.7. Waist Circumference. Waist (abdominal) circumference is an anthropometric indicator of deep adipose tissue. Measurements will be done over bare skin or underwear using a flexible, inelastic fiberglass tape measure marked in centimeters. Waist circumference will be measured at the minimum circumference, usually the umbilicus, between the iliac crests and lower ribs.

8.4.8. Food frequency questionnaire. Food intake will be assessed using a self-administered Block food frequency questionnaire to allow quantification of total energy intake and percent calories from fat. These data will be used to estimate dietary change and to provide information about adherence of participants to the weight loss program.

8.4.9. Physical activity. The Paffenbarger Activity Questionnaire[58] will be administered as a measure of physical activity. This questionnaire has been used to assess leisure time activity in many studies and can be scored to provide an estimate of calories expended per week in overall leisure time activity and in activities of light (5 kcal/min), medium (7.5 kcal/min), and high (10 kcal/min) intensity. Changes in exercise on the questionnaire have been shown to be predictive of weight change in overweight and obese individuals. Physical activity will be used to characterize adherence to the weight loss intervention and will be examined as a potential predictor of successful weight maintenance.

8.4.10. Sleep questionnaire. We will assess sleep quality using established and validated instruments, the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness using the Epworth Sleepiness Scale (ESS) that are the standard for sleep research. The PSQI is a 19-item questionnaire that measures reported sleep patterns and sleep problems, including sleep quality, sleep latency, sleep efficiency and napping behavior.

8.4.11. Quality-of-life Measurements

Incontinence Impact Questionnaire. The Incontinence Impact Questionnaire is a validated instrument that measures the impact of incontinence on social

activity, physical activity, travel, and emotional health on a 4-point Likert scale, with the sum of responses transformed into a score on a 0-100 continuous scale.

Urogenital Distress Inventory. The Urogenital Distress Inventory is a validated instrument that has been used extensively in incontinent populations to quantify incontinence symptom bothersomeness.[59] The degree of bothersomeness of irritative, obstructive/discomfort, and stress symptoms is recorded on a 4-point Likert scale with the sum of responses transformed into a score on a 0-100 continuous scale.

Short Form 36. The Short Form 36 is a 36-item measure that was drawn from the 149-item full set of the Medical Outcomes Study (MOS) Functioning and Well-Being Profile.[60, 61] Two summary scales can be calculated, the physical component summary and the mental component summary.[61] The physical component summary subscale addresses the areas of greatest importance to women with both incontinence and overweight and obesity. Large differences in change scores on this subscale have been observed when overweight and obese women reduce weight[62, 63] and with improvement in incontinence severity.

Participant satisfaction with health. We will include a rating of satisfaction with changes in incontinence used in prior incontinence treatment studies.[35, 36] This is a self-report ordinal scale and measures how participants feel about their treatment outcomes.

Beck Depression Inventory. The Beck Depression Inventory [64] is a 21-item self-reported measure of depressive symptoms. It will be used in our study to assess changes in depressive symptoms related to randomization to the weight loss intervention, to the motivation-based weight maintenance program, and to changes in weight and frequency of incontinence.

8.4.12. Other Measurements. Variables that may act as predictors or moderators of the efficacy of weight reduction for reducing the frequency of incontinence will be documented at baseline. These covariates include demographic characteristics (age, race/ethnicity, relationship status, education, annual family income), general health, genitourinary history (duration of incontinence, prior type and duration of therapy, amount of urine loss, pad use, drinking habits), reproductive health (gravity, parity, route of delivery, menopause status, hormone therapy use), medical history (hypertension,

pulmonary disease, stroke, diabetes, surgical history (hysterectomy, pelvic organ prolapse repair, other pelvic or abdominal surgery), and medications.

8.4.13. Ensuring Objective Assessments. Throughout the study every effort will be made to ensure objective and blinded assessments of outcomes. Although participants will be told the name of their treatment assignment they will not be provided details about the intervention techniques of the other treatment groups. Focus will instead be maintained on the support group to which they are assigned.

Staff who review the voiding diaries and record participant weight at the 6, 12 and 18 month assessments will not be informed of the participant's treatment assignment and will not participate in the delivery of the study interventions. Likewise, staff who perform the urodynamic studies will not be informed as to the participant's treatment assignment. Care will be taken to avoid overtly identifying treatment assignments on participant charts.

9.0 Study Interventions

9.1 Incontinence Information**.** At the randomization visit, all participants will receive a booklet that includes information commonly given to incontinence patients in clinical practice entitled "Staying Dry: A Practical Guide to Bladder Control - Patient Instruction Booklet". The booklet presents information about urge and stress incontinence, how to locate the pelvic floor muscles, daily pelvic floor muscle exercises, use of pelvic muscles to avoid urine loss and strategies for managing symptoms of urinary urgency.

9.2 Education for the Control Condition. In addition to the incontinence self-help booklet, women randomized to the control condition (entitled the "Structured Education Program"), will be invited to participate in hour long group educational sessions at months 1, 2, 3, and 4. At months 6, 9 and 15, the groups will meet again for informational sessions. The content of these education and support sessions will include information about weight loss, physical activity, healthy eating habits and general health promotion.

9.3 Weight Reduction Program (Months 1-6). Participants in the weight reduction program (entitled the "Lifestyle and Behavior Change Program") will receive an intensive group-based behavioral weight reduction program. They will be taught specific cognitive and behavioral skills to assist in the

modification of their eating and exercise habits. Participants will meet weekly for 6 months in group-sessions led by a nutritionist, exercise physiologist, or behaviorist and will follow a structured protocol. Therapists will not discuss incontinence during the weight reduction program. With this intervention, women are expected to lose an average of 7-9% of their initial body weight in 6 months. The central components of the weight loss program are:

Diet: All participants will be placed on a standard caloric diet (e.g., 1200-1500 kcals/day, depending on initial body weight). The dietary recommendations in this study (< 30% of calories from fat; < 10% of calories from saturated fat) are consistent with the recommendations of the American Heart Association, the American Diabetes Association, and the American College of Sports Medicine.[65-67] To help participants initially meet their calorie and fat goals, sample meal plans modeling appropriate food selections will be provided and meal replacement products will be recommended and/or provided to participants. A fat/calorie guidebook will also be given to each participant to be used in the self-monitoring of food intake. Participants will be instructed to monitor food and beverage intake daily.

Exercise: All participants will be encouraged to gradually increase their physical activity until they are exercising 40 minutes per day on 5 days per week. Participants will be encouraged to exercise on their own at home using brisk walking or activities of similar intensity to brisk walking as their primary form of physical activity. Since lack of time is considered the greatest barrier to exercise, participants will be encourage to accumulate the amount of exercise necessary each day by engaging in multiple short bouts of activity (e.g., at least 10 minutes in length). Participants will be instructed to self-monitor their exercise daily. Pedometers will be provided and participants will be encouraged to gradually increase their activity to 10,000 steps per day.

Behavioral skills: To encourage the adoption of the above dietary and physical activity recommendations, the following skills will be introduced in the initial phase of treatment:

- *Self-monitoring*
- *Stimulus control*
- *Problem-solving*
- *Assertiveness training*
- *Social support*
- *Goal setting*
- *Cognitive restructuring*
- *Relapse prevention*

9.4 Weight Maintenance Interventions (Months 7-18). After 6 months of weight reduction intervention, women in the Lifestyle and Behavior Change Program will be cluster randomized at each site by weight reduction counseling group to a skill-based or motivation-based weight maintenance program. Both 12-month maintenance programs will involve group meetings every two weeks. The programs will be matched on contact frequency and duration. The programs will differ in their treatment focus.

9.4.1. Skill-based Approach to Maintenance. The skill-based approach is similar to what is commonly taught in the maintenance phase of standard behavioral weight loss programs. In the skill-based group, months 7-18 of treatment will focus on refining the cognitive and behavioral skills acquired in the first 6 months of treatment. Topics presented in the first 6 months of treatment will be revisited, expanded and refined. The overall goal will be to practice the skills acquired in the first 6 months of treatment so they increasingly become "habits" and to help participants apply these skills in a variety of situations that will occur over the year of maintenance.

9.4.2. Motivation-based Approach to Maintenance. The focus of treatment in the motivation-based group in months 7-18 will be to increase and sustain motivation to utilize the dietary, physical activity, and behavioral skills already acquired. Group sessions will be devoted to the introduction and discussion of exercises designed to 1) increase participants' satisfaction with their weight loss and incontinence outcomes, 2) decrease participants' ambivalence about their current behavior change efforts, 3) increase participants' investment in behavioral choices, and 4) increase participants' motivation to maintain their new eating and exercise behaviors. Examples of specific group topics and exercises are:

- *Personalized reminders of baseline state*
- *Motivational interviewing*
- *Personal investment in new behaviors*
- *Self-reward*

9.5 Retention of Study Participants

Every effort will be made to retain participants through the 18-month follow-up period. Based on prior experience at the two Clinical Centers, we expect 95% (or 314) of the 330 women to complete the 6-month assessment and 85% (n=280) of participants to complete the 18-month assessment.

The investigative team will encourage retention in PRIDE by educating participants about the importance of the study, encouraging excellent staff-participant rapport, and promoting participant loyalty and identification with PRIDE. Birthday and anniversary notices will be sent and friendly and efficient Clinical Center environments will be maintained. Identifying information including address, phone number, social security number and the name, address and phone number of one family member and two close friends able to locate the subject will also be obtained prior to randomization to facilitate participant-staff contact. Identification with PRIDE will be promoted via the periodic newsletter, refrigerator magnets with the PRIDE logo, and an annual social event for study participants. Participants will be given a stipend of $25 at both 6 and 12 months and $50 at 18 months for completing these assessment visits. The coordinating center will monitor the retention rate at all clinics, identifying problems, proposing solutions, and reporting on these matters to the Steering Committee and to the Data and Safety Monitoring Board.

10.0 Serious Adverse Events

The diet and exercise intervention in PRIDE was designed to encourage gradual weight loss in the context of a healthy lifestyle and should pose no added risk to overweight or obese participants. Only serious adverse events as defined by the Food and Drug Administration (death, life-threatening event, inpatient hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity) will be routinely ascertained in this trial. Important medical events may be considered serious adverse experiences at the discretion of the site Principal Investigators if they might jeopardize the participant or

might require medical or surgical intervention to prevent one of the outcomes defined as serious.

Safety-related events will be reported in a timely fashion as required by the Data and Safety Monitoring Board and the IRB.

11.0 Data Management

11.1 Data Collection

The Coordinating Center will develop machine-readable data forms using Cardiff Teleform software. Data forms will be filled out at the clinical sites and sent to the Coordinating Center (CC) via standard fax machines. At the CC, the forms will be received on a server that will use optical character reader (OCR) technology to acquire the data. A CC operator will verify the data manually on screen. This important step corrects many misinterpretations in the automated data input. Verified data are then sent over the local area network (LAN) at the CC to a database on a Microsoft SQL Server. Analog images of the forms are stored in an image-management system on optical disk. The CC does not receive any paper in the process of data acquisition.

11.2 Data Processing

All of the study data are subject to a set of daily error-checking programs. This routine includes checks for completeness, data consistency, and invalid ranges. The results are posted to the study website where clinical site personnel check daily to confirm that the CC has received all of the faxed forms and to address any queries.

A password-protected web site will be the study's data collection hub. Computers at the clinical centers will access a secure and private UCSF CC web server that provides continually updated data summary reports. All reports available on the website will be generated on demand in real time from current study data. The Coordinating Center will provide user accounts and security-enabled web browsers for all clinical center staff.

Clinical centers will respond to queries and edit data forms on the website. As part of the data editing system, the website will also include pages that closely resemble the questionnaires so that clinical staff can view the data that has been accepted into the data system.

Clinical sites will access their data via these pages and address queries. Access to these pages will be restricted to authorized personnel.

12.0 Statistical Analysis, Sample Size And Power Estimates

12.1 General Analysis Considerations

12.1.1. Analysis strategy. The primary analyses will be by intention-to-treat, without regard to adherence to intervention protocols. The major outcome for several of the specific aims are change from baseline in frequency of incontinence episodes, body weight or quality of life. Our primary analysis approach will use mixed linear regression models [68, 69] to compare the average changes in the intervention and control groups. We will control for Clinical Center as a fixed effect in all analyses. Interactions of the outcomes with Clinical Center will be assessed in exploratory analyses.

12.1.2 Cluster effects. Weight loss groups of 10-20 women will be assembled immediately after randomization and preserved in the second randomization, by group, to motivation-based or skill-based maintenance. There may be correlation of outcomes for members of these groups that would reduce precision and power, increasing sample size requirements. This can be summarized as the design effect, or the ratio of the required sample size to the sample size that would be needed if there were no correlation of outcomes within small groups. Mixed linear models will be used to account for correlations within intervention groups. Fit by restricted maximum likelihood and implemented in SAS Proc Mixed, this method is powerful and accommodates the complex covariance structures that will arise, which will differ by treatment arm. It is also robust to moderate departures from multivariate normality,[70] but normalizing transformations of the outcome variables will be developed as necessary.

Potential complications due to dropout. In studies of weight loss, participants who drop out early typically regain most or all the lost weight. Under the hypotheses motivating this study, this would imply that most or all improvements in incontinence will also be eroded among study dropouts. The first line of defense in this trial will be to minimize the dropout rates, and to attempt to obtain outcome measurements on participants who are no longer participating in the weight loss intervention. In addition, current practice in

weight loss studies is to impute baseline outcomes for observations missing due to dropout, substantially reducing bias due to "non-ignorable" missingness.[71, 72] A slight drawback of this procedure is that such singly imputed values are treated as known, so that standard errors on average are too small. To address this potential source of inferential error, we will use multiple imputation of the baseline outcomes with an additive error term derived from the repeated measures model estimate of within-subject residual error. The analysis will then be carried out in the multiple datasets, and the results combined using standard methods to produce summary effect and standard error estimates that properly incorporate the imputation error.[71, 72] As a sensitivity check, we will also carry out a secondary analysis without imputation, but adjusted for baseline covariates, under the assumption that the data are missing at random [71] given treatment assignment, the observed outcome values, and baseline predictors of outcome.

12.2 Statistical Methods

12.2.1. Specific Aim #1. *To determine whether randomization to a weight reduction program results in greater reductions in frequency of incontinence episodes at 6 months compared to the control condition.*

Analysis. Our hypothesis is that randomization to the weight reduction group will result in greater reductions in frequency of incontinence compared to the control group. The predictor variable is assignment to the weight loss or control group and the outcome is change from baseline to the end of the weight loss intervention at 6 months in number of incontinent episodes per week, as recorded on the 7-day voiding diary. As described above, we will use mixed linear regression models to compare average changes in the intervention and control groups, controlling for clinical center and taking account of clustering within weight loss groups.

Sample size estimation. In our pilot study of weight loss for treatment of incontinence, the between-group difference in reduction in incontinence frequency was 12 episodes per week (average reductions of 14 vs 2 episodes in the weight loss vs. control groups), with standard deviation (SD) of 14 episodes per week, for a very large standardized effect size of nearly 0.9 SDs. In the proposed study, expected weight loss will be smaller and the control group will receive a self-help booklet that will likely result in some improvement in

incontinence; furthermore the pilot study was small, providing imprecise estimates. Thus, we conservatively assume a smaller net reduction in incontinence frequency of 6 episodes per week in the weight reduction compared to the control group, half the effect seen in the pilot study but large enough to be clinically meaningful. This corresponds to a standardized effect size of .43 SDs, assuming an SD of 14 episodes per week for the changes in frequency. We also assume that 10% of the sample will drop out before the 6-month visit; with imputation of baseline values for missing post-randomization incontinence frequencies, this attenuates the effect size in proportion to the dropout rate. Finally, we assume that clustering within the small intervention groups will induce a moderate design effect of 1.3. We adapted standard methods for two-sample comparisons of a continuous outcome to account for the design effect as well as the attenuation of the treatment effect size by imputation of baseline values. Under these assumptions, a sample of 330 women will provide at least 80% power in two sided tests with alpha of 5% to detect between-group differences of 6 incontinence episodes per week. Small to moderate gains in power may be obtained by the use of repeated measures, depending on the level of within-subject correlation.

12.2.2. Specific Aim #2. *To determine if randomization to a motivation-based maintenance program results in less weight regain from 6 to 18 months compared to a skill-based maintenance program.*

Analysis. Our hypothesis is that motivation-based weight maintenance will result in less weight regain than skill-based weight maintenance over the 12 months of the intervention. The predictor variable is random assignment to the motivation-based weight maintenance program compared to skill-based weight maintenance or control group, and the outcome is change in weight from the end of the weight reduction program at 6 months to the end of the maintenance period at 18 months. As in Specific Aim #1, we will use mixed linear regression models for change in weight over the maintenance period, controlling for group, degree of weight loss during the weight loss period, and taking account of clustering by weight loss group.

Power estimates. Conservatively assuming a loss to follow-up of 15% between 6 and 18 months, the sample of 220 women randomized to motivation-based or skill-based maintenance strategies will provide 80% power to detect between-group differences in weight loss of 0.56 standard deviations. In prior TRIM

weight loss studies,[73] the standard deviation of weight loss at 18 months in the skill-based behavioral treatment condition was 6.8 kg, so that the minimum detectable between-group difference in average weight loss at the end of the study will be less than 3.8 kg.

12.2.3. Specific Aim #3. *To identify women who are most likely to experience improved continence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed).*

Analysis. Our hypothesis is that some subgroups of women (defined by baseline body weight, body mass index, waist circumference, or type of incontinence), will be more likely to have improvement in incontinence with weight loss compared to others. Analyses in subgroups defined by these baseline variables will be similar to those described for Specific Aim #1. These subgroup analyses constitute comparisons between randomized groups, and are only mildly affected by the multiple comparisons problem. We will test for subgroup by treatment interactions.

Power estimates. Under the same assumptions used for Specific Aim 1, subgroups comprising 50, 40, or 30% of the sample will provide 80% power to detect standardized effects of approximately 0.58, 0.63, and 0.75 SDs, respectively, corresponding to changes of 8.5 to 10.5 episodes of incontinence per week.

12.2.4. Specific Aim #4 *To determine if randomization to a weight reduction program results in greater improvement in continence from baseline to 18 months compared to control and whether the motivation-based maintenance program results in greater improvements in continence than the skill-based maintenance program or control from baseline to 18 months.*

Analysis. Our hypotheses are that the weight reduction program will result in lower frequency of incontinence overall than in the control condition, and that motivation-based weight maintenance will result in lower frequency of incontinence than skill-based weight maintenance during the 18 months of follow-up. The predictor variables are random assignment to the weight

reduction program or to the motivation-based weight maintenance program compared to skill-based weight maintenance, or to the control group, and the outcome is change from baseline to the end of the weight loss intervention at 18 months in frequency of incontinence episodes. Analyses will be similar to those described above for specific aim 1.

12.2.5. Specific Aim #5. *To determine if randomization to a weight reduction program results in greater improvement in quality of life from baseline to 6 and 18 months compared to the control condition.*

Analysis. Our hypothesis is that randomization to a weight reduction program will result in greater improvements in quality of life measures than to a control condition at both 6 and 18 months of follow-up. The predictor variable is assignment to the weight reduction or control groups and the outcome is change in quality of life outcomes including Incontinence Impact Question (IIQ), Urogenital Distress Inventory (UDI) and Short Form-36 (SF36), from baseline to 6 and 18 months. Analyses will be similar to those described above for specific aim 1. In addition to the primary analysis comparing weight reduction to a control condition, we will also make pairwise comparisons between motivation-based maintenance, skill-based maintenance, and the control condition at 18 months.

Power estimates. Under the assumptions used for Specific Aims 1 and 2, the sample of 330 women will provide 80% power to detect actual treatment differences of 0.43 SDs in the primary comparison between weight loss and control at 6 months, and 0.49 SDs at 18 months. In pairwise comparisons between the three groups at 18 months, we will be able to detect differences of 0.56 SDs. These are small to moderate differences, as shown below.

Instrument	**SD of single measures**	**Minimum detectable difference in changes****
UDI	50[59]	22-28
IIQ	60[59]	26-34
SF36 PCS*	25-30[63]	16-18
BDI	4.5[74]	19-25

* Physical component scale

** Assuming within-subject correlation of repeated measures of 0.5

In all cases, smaller between group differences in change would be detectable if within-subject correlation exceeds 0.5.

12.3 Exploratory analysis of potential mechanisms for improvement in incontinence with weight loss. A series of closely related mixed linear models will be used to assess mechanisms by which the weight reduction intervention potentially affects measured incontinence frequency as well as related quality of life measures. We will first assess modification of the effects of treatment by baseline urodynamic measurements of leak point and intravesical pressures, to determine if the effectiveness of the weight reduction intervention varies by these parameters. To maximize efficiency, effect modification will be assessed as a continuous interaction between treatment assignment and the urodynamic measures. We will then examine the overall effects of assignment to the weight reduction group on the urodynamic measures as well as weight loss, to show the effect of the intervention on the proposed mediators. Next, we will use repeated measures models to determine the association between change since baseline in the proposed mediators and current incontinence frequency, to show that changes in the mediator are associated with changes in the primary outcome, and to determine which of the proposed mediators independently predict change in incontinence frequency. Finally, we will examine the attenuation of the estimated effect of treatment on incontinence frequency after controlling for changes in the proposed mediators, as an estimate of the proportion of the treatment effect explained. Confidence intervals for proportion of the treatment effect explained will be computed.[75]

13.0 Study Organization and Governance

PRIDE will be conducted at two Clinical Centers with extensive experience in recruitment of obese and overweight persons and in administering successful weight reduction programs (The Miriam Hospital/Brown Medical School and the University of Alabama). The trial will be coordinated at the Women's Health Clinical Research Center at the University of California, San Francisco. The Steering Committee will be the primary governing body of the study and will be comprised of the Principal Investigators from the Clinical Centers, a behavioral consultant from the University of Arkansas, the Principal Investigator and Co-Principal Investigator of the Coordinating Center and project scientists from

NIDDK. In the development stage of PRIDE, the Steering Committee will direct refinement of the study design, completion of the protocol, and development of interventions, operations manual and data collection forms. As recruitment and enrollment begin, the Steering Committee will monitor study progress and quality, and resolve issues that arise during follow-up. Finally, the Steering Committee will review and approve proposals for ancillary studies, analyses, scientific presentations and manuscripts.

A Data and Safety Monitoring Board (DSMB) will be organized by the Project Office of the NIDDK. The DSMB will convene at the end of protocol development to review the protocol and develop guidelines for DSMB activities and stopping rules. They will meet 6 months after recruitment begins then approximately annually to review study progress, oversee participant safety, monitor data quality, and provide operational and technical advice to the Steering Committee and the NIDDK project officer. The DSMB will be comprised of five members with expertise in operational and biostatistical aspects of clinical trials, urinary incontinence and weight reduction. No member of the DSMB will participate in the study as an investigator or be involved in any way in the conduct of the study.

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PRIDE – Urodynamic Study Protocol

A substudy to the **P**rogram to **R**educe **I**ncontinence by **D**iet and **E**xercise (PRIDE): an NIDDK-sponsored, multi-center, randomized, controlled clinical trial comparing incontinence improvement between groups randomized to a weight reduction program or control in overweight or obese women with urinary incontinence

First Revision: 9/3/04

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SIGNATURE PAGE

FINAL PROTOCOL SIGNATURES:

	Name	Signature	Date
Investigator	Leslee Subak, MD		
Investigator	Holly Richter, MD		
Investigator	Deborah Myers, MD		
Principal Investigator	Deborah Grady, MD, MPH		

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1.0 BACKGROUND AND RATIONALE

Urinary incontinence is a prevalent health condition in women and has a significant impact on quality of life. Over 13 million Americans, including 25% of reproductive age women and up to 50% of postmenopausal women, are affected by stress (involuntary loss of urine with coughing, sneezing, straining, or exercise), urge (loss of urine associated with a strong need or urge to void) or mixed incontinence (episodes of both types).[1-3] Epidemiological studies suggest that obesity is a strong risk factor for urinary incontinence[4-7] and early observational[8, 9] and small cohort studies[10, 11]suggest that weight reduction may be an effective treatment for incontinence.

PRIDE — The **Program** to **Reduce Incontinence** by **Diet** and **Exercise** is a multicenter, randomized, clinical trial evaluating weight reduction as an innovative treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized to either a 6-month behavioral weight reduction program or control (instructional handouts and brief informational sessions on diet and exercise) and followed for 18 months. At baseline, all women will be given a pamphlet describing a self-administered behavioral treatment program for incontinence. **In a subgroup of 100 women, we will perform standardized pelvic floor evaluation and urodynamic studies at baseline and at 6 months to elucidate the mechanism by which weight loss improves incontinence.**

2.0 CLINICAL TRIAL OBJECTIVES

The primary aims of PRIDE are:

1. to determine whether randomization to a weight reduction program results in greater reductions in frequency of incontinence episodes at 6 months compared to control;
2. to identify women who are most likely to experience improved continence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed).

As a part of PRIDE we plan to:

1. conduct exploratory analyses to evaluate whether baseline urodynamic measures can identify women who are most likely to experience improved continence after weight reduction and;
2. investigate the mechanism by which weight loss improves continence by examining the relationship of improvement in continence and changes in urodynamic measures.

To achieve these aims, the pelvic floor evaluation and urodynamic testing (UDS) will be performed on the first 50 volunteers at each site who agree and sign a separate informed consent. Standardized urodynamic testing will take place at baseline and again at the 6-month follow-up study visit.

3.0 STUDY DESIGN

100 overweight or obese women with urinary incontinence will undergo pelvic floor evaluation and urodynamic testing at baseline and at 6 months, following completion of either the 6-month weight reduction program or control. Women participating in PRIDE will be randomized in a 2-to-1 ratio to either of these treatment groups and it is expected that the randomization pattern will be reflected in the Urodynamic Substudy. (Please see the PRIDE Protocol for a complete description of the PRIDE study.)

3.1 STUDY TIMELINE

The first year of the study will include developing and refining the protocols, operations manual, forms, database, intervention materials and websites. Participant recruitment will begin in the first year and continue for approximately two years. The UDS evaluations will begin in year 2.

4.0 STUDY SITES

The study will be conducted at two clinical centers and three institutions: Miriam Hospital and Brown University, Providence, RI and the University of Alabama, Birmingham, AL. Data will be collected, managed and analyzed at the Women's Health Clinical Research Center, University of California at San Francisco, San Francisco, CA. A list of investigators is available at the PRIDE public website at: http://coordinatingcenter.ucsf.edu/pride/

5.0 STUDY POPULATION

5.1 SAMPLE SIZE

Of the 330 volunteers for PRIDE, the first 100 women who agree to participate in the Urodynamic Study will be enrolled (approximately 50 at each of 2 clinical centers).

5.2 INCLUSION AND EXCLUSION CRITERIA

All participants must first meet the entry criteria for PRIDE and must sign an additional informed consent form for the Urodynamic Study. Because of weight limits for the urodynamic testing chairs and difficulty performing the evaluation in very obese women, participants with weight < 300 pounds are eligible for this sub-study.

6.0 ETHICS

6.1 INSTITUTIONAL REVIEW BOARD

The study protocol, informed consent form, study questionnaires, educational and recruitment materials must be approved by the Institutional Review Board at each institution prior to the start of the study. Protocol amendments generated during the study must be approved by the IRBs prior to their implementation. Copies of all IRB approval letters will be sent to the Project Office at the NIDDK. Reports issued by the PRIDE Data and Safety Monitoring Board will be distributed to the investigators to be forwarded to their IRBs. Any serious adverse events that occur during the trial must be reported to each IRB.

6.2 INFORMED CONSENT FORM

The UDS informed consent form will explain in lay language the goals of the substudy, the visits and procedures and the risks and benefits of participating. Any amendment to the protocol generated during the study that impacts participants will be reflected in a revised consent form that must be signed by the participant.

7.0 STUDY SCHEDULE AND PROCEDURES

7.1 ENROLLMENT PROCEDURES

7.1.1 *Enrollment in the UDS substudy*

Women enrolling in PRIDE will be randomly allocated in a 2-to-1 ratio to either the weight reduction program or control condition. Prior to randomization, women will be asked to participate in the UDS substudy. A volunteer sample will be included. After the first 30 women are enrolled in the UDS substudy, we will evaluate the sample to assess the distribution of group assignment (weight loss or control condition), incontinence type and BMI. We will classify incontinence type as 1) stress only or mixed stress incontinence

and 2) urge only or mixed urge incontinence. Our goal is to have a UDS substudy sample with approximately 67% women in the weight loss group, 50% with stress/mixed stress incontinence, and 50% with BMI < 35 kg/m^2. If there is >10% deviation from these goals, we will consider limiting enrollment in the UDS study to underrepresented intervention group, incontinence type or BMI category.

7.1.2 *Ensuring Objective Assessments*

Throughout the study every effort will be made to ensure objective and blinded assessments of outcomes. Staff who performs urodynamic studies will not be informed of the participant's treatment assignment. Care will be taken to avoid overtly identifying the treatment assignments on participant charts.

7.2 STUDY VISITS

7.2.1 *Recruitment*

All women who are eligible and agree to participate in PRIDE will be offered the option of undergoing pelvic floor evaluation and urodynamic testing. The UDS substudy will be explained fully after the woman has completed her second screening visit. Those who agree to participate will be scheduled for a UDS visit in addition to the main study baseline visit.

7.2.2 *Urodynamic Study Visits*

At the baseline and at the 6 month urodynamic visits, a urogynecologist, or a designee under her supervision, will perform the pelvic floor evaluation using the Brink's score of pelvic muscle strength, Pelvic Organ Prolapse Quantification (POP-Q), and urethral hypermobility (Q-tip test) and the urodynamic studies including cough stress test, passive uroflowmetry and filling cystometrogram,. Measurements, diagnoses, and terms will conform to the recommendations of the Committee on Standardization of Terminology of the International Continence Society and will use the same methods as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Urinary Incontinence Treatment Network studies.[12]

7.3 URODYNAMIC STUDY PROCEDURES

Urinalysis. A urine dipstick test for urinary tract infection will be done prior to the pelvic floor evaluation and UDS procedures. When there is suspicion for infection, the remainder of the urodynamic substudy evaluation will be postponed until the infection has been treated.

The Brink's test assesses pelvic muscle strength by scoring perceived pressure on the examiner's finger, alteration of the vertical plane, and contraction time. [13] Using sterile gloves and lubricant jelly the examiner inserts one or two fingers into the participant's vagina and instructs the participant to squeeze the pelvic muscles. Any degree of flicker on the examiner's finger(s) is considered evidence of ability to contract the muscle. This test will assess three elements of the pubococcygeus muscle contraction: pressure, duration (using a stop watch that is accurate to the tenth of a second), and displacement.

The Pelvic Organ Prolapse Quantification (POP-Q) is a standardized description of the severity of pelvic organ prolapse with good inter- and intra-observer reliability for prolapse staging.[14-17] This procedure will be performed according to the guidelines established by the International Continence Society[18] and will be standardized as demonstrated in a videotape produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Exam"). Any prolapse will be noted and the maximum anterior-posterior length with maximum straining of the genital hiatus and perineal body will be measured and recorded. The six primary measuring points are defined in the International Continence Society's standardization report and a detailed description is included in the PRIDE Operations Manual. Total vaginal length will be recorded.

The Q-tip test will be used to evaluate mobility of the urethra and bladder neck. A sterile, lubricated cotton or dacron swab (Q-Tip) is placed into the urethra until it lies just within the urethrovesical junction. The angle circumscribed by the distal end of the swab relative to the horizontal at rest and during maximum Valsalva effort is measured with a Robinson Pocket goniometer. Bladder neck hypermobility is defined as a resting angle >30^{o} or maximum straining angle >30^{o}.[19, 20]

The Cough Stress Test will be performed to determine the presence and degree of stress incontinence. Stress tests that are positive in the face of positive urine cultures will be repeated when the infection is resolved. After the participant voids, the bladder is emptied completely using a 12 French catheter. Then the bladder is retrograde gravity filled to 300 ml or maximum capacity, whichever is less and the catheter is removed. In the supine position, the participant is asked to Valsalva and cough. If no

leaking is noted, the participant stands and is asked to Valsalva and cough. Participants with Stage III or IV anterior prolapse who have a negative cough stress test (do not leak) will have their prolapse reduced (instructions detailed in the PRIDE Operations Manual) and provocative maneuvers will be repeated. Stress incontinence is considered present when the participant demonstrates transurethral urine leakage with or immediately after increased intra-abdominal pressure (with Valsalva effort or coughing).

Non-Instrumented Uroflowmetry (NIF) is performed after the 300 cc cough stress test to measure maximum urine flow rate, mean flow rate, time to maximum flow, and voided volume. Any of the electronically derived methods of calculating the uroflowmetry values are acceptable. The uroflowmeter should be calibrated in accordance with routine clinical site practice standards and the scale should be set to zero prior to the start of each participant's study. The participant will void into the uroflowmetry machine while in the sitting position on the Uroflow chair and a time-flow curve is recorded using a standard urodynamic recorder. Flow pattern is classified as either normal (continuous, smooth and arc shaped with high amplitude) or abnormal (doesn't meet these criteria). Post-void residual (PVR) volume will be measured with a catheter.

A Filling Cystometrogram (CMG) will be performed to measure intravesical pressure (Pves), intra-abdominal pressure (Pabd), and subtracted detrusor pressure (Pdet). With the participant sitting in a 45 degree reclined position, the fluid-filled column-type tubing will be connected to a dual lumen 8 French catheter. An intravesical catheter will be placed and the bladder filled with room temperature saline or sterile water at a rate of 50 ml/min. A rectal catheter will be used to measure continuous intra-abdominal pressure. Pressures will be continuously recorded on a multichannel urodynamics recorder throughout the conduct of the CMG. Flow rate and volume will also be recorded continuously.

Bladder Sensation Parameters: Three bladder sensation parameters will be measured during filling cystometry. The participant is instructed to state when she has the sensation of 1) first desire to void, 2) strong desire to void, and 3) sensation of maximum cystometric capacity, using standardized definitions/descriptions.

To assess proper placement of catheters the participant is instructed to cough at various times during the cystometrogram and the examiner will then record the Valsalva Leak Point Pressure (VLPP) or absolute intravesical pressure during the Valsalva maneuver that produced leakage.

Procedures will differ slightly according to the presence or absence of Stage III or IV anterior prolapse and examiners will follow instructions detailed in the PRIDE Operations Manual.

The following data points for the CMG will be calculated by the UCSF Coordinating Center for each participant prior to analyses:

- Bladder compliance *[Maximum Cystometric Capacity (MCC)/ (Pves at MCC - Pves at baseline)]*
- Mean of VLPP values obtained for unreduced and reduced measurements *mean Pves = (Pves 1 + Pves 2 + Pves 3) / 3 or mean Pves = (Pves 1 + Pves 2) / 2*
- VLPPs from different baselines with and without reduction *(mean Pves - Pves at baseline)*

8.0 QUALITY CONTROL STANDARDS

The POP-Q test is performed according to the guidelines established by the International Continence Society[18]. The Brink's and Q-Tip tests will be performed by accepted guidelines and following techniques instituted by the Urinary Incontinence Treatment Network (UITN) UDS Working Group.

Several testing standards have been established by the UITN UDS Working Group in an effort to minimize variability of UDS completion and interpretation across Testers / Observers. The PRIDE UDS standards follow recommendations of the ICS Standardization Committee of Good Urodynamic Practice recently published by Schafer and others.[21] Both sites will use water perfusion catheters with baseline zeroing to atmospheric pressure. They will provide to the Coordinating Center copies or duplicate originals of tracings, graphs and output from the urodynamic studies.

Standards for Signals (AKA: tracings, graphs, recorder output)

An original printout of the UDS signals (tracings) should be retained in the participant's research record and another printout (preferably another original) should be mailed to the central repository at the UCSF Coordinating Center (CC) along with all other required source documentation. (Participant names should be masked before transmission. Unique code numbers will be used to identify participant records.) UDS data will be transmitted to the repository electronically following data management and data transmission procedures described elsewhere.

A) **Graph scaling**: the scaling of the signals will be standardized across centers

and kept unchanged as much as possible. Urodynamic quality control is dependent on the tester's ability to recognize patterns, and the recognition of patterns is greatly improved by standard scaling of the signals.

B) **Labeling**: The signals of each respective study will be **clearly labeled;** i.e. non-instrumented uroflowmetry (NIF) vs. CMG, to simplify a central review. The CC will provide a labeling system for sites.

C) **Annotation:** The signals will be annotated in accordance with the required PRIDE data points.

Interpretation of the UDS and completing the PRIDE Data Form

A PRIDE Physician Investigator must verify, validate and confirm that the UDS was completed in accordance with sound clinical practice and in compliance with the PRIDE UDS protocol. To minimize invalid and missing data, a PRIDE Physician Investigator and/or certified examiner will review the UDS signals prior to removal of the catheters. If valid UDS data points cannot be abstracted from the signals, studies should be repeated whenever clinically feasible.

UDS data points that are artifactual, not interpretable, or deemed invalid by the PRIDE Physician Investigator will not be recorded on the PRIDE Data Form. If studies cannot be repeated, these data fields will be filled with a special missing values code to indicate the data are deemed invalid.

9.0 SERIOUS ADVERSE EVENTS

The risk of urodynamics testing is minimal. Serious adverse events as defined by the US Food and Drug Administration (death, a life-threatening event, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability or incapacity) will be routinely ascertained in this trial. Important medical events may be considered serious adverse experiences by the clinical site investigator if the event might jeopardize the participant or might require medical or surgical intervention to prevent one of the outcomes defined as serious.

Safety-related events will be reported in a timely fashion as required by the Data and Safety Monitoring Board and the IRB.

10.0 DATA MANAGEMENT

10.1 DATA COLLECTION

Data forms will be filled out at the clinical sites after each of the urodynamic study visits and sent to the Coordinating Center via standard fax machines. Detailed instructions will be provided in the PRIDE Operations Manual.

10.2 DATA PROCESSING

All study data are subject to a set of daily error-checking programs. This routine includes checks for completeness, data consistency, and invalid ranges. The results are posted to the study website where clinical site personnel check daily to confirm that the CC has received all of the faxed forms and to address any queries.

A password-protected www site will be the study's data collection hub. Computers at the clinical centers will access a secure and private UCSF CC www server that provides continually updated data summary reports. Staff at clinical centers will edit data forms on the website. Access to these pages will be restricted to authorized personnel.

10.3 DATA CONFIDENTIALITY

Participant information is transmitted to the PRIDE Coordinating Center on data forms on which the participant is identified by a code number only. Participant names are confidential and only the clinical site staff will retain files that identify participants by name. Participant names on raw data that will be transmitted to the Coordinating Center (such as UDS recordings) must be blacked out and the participant's code number must be written on the recording instead.

11.0 STATISTICAL ANALYSIS

This will be an exploratory analysis of potential mechanisms for improvement in incontinence with weight loss. A series of closely related mixed linear models will be used to assess mechanisms by which the weight loss intervention potentially affects measured incontinence frequency as well as related quality of life measures. We will first assess modification of the effects of treatment by baseline urodynamic measurements of leak point and intravesical pressures, to determine if the effectiveness of the weight loss intervention varies by these parameters. To maximize efficiency, effect modification will be assessed as a continuous interaction between treatment assignment and the urodynamic measures. We will then examine the overall

effects of assignment to the weight loss arm on the urodynamic measures as well as weight loss, to show the effect of the intervention on the proposed mediators. Next, we will use repeated measures models to determine the association between change since baseline in the proposed mediators and current incontinence frequency, to show that changes in the mediator are associated with changes in the primary outcome, and to determine which of the proposed mediators independently predict change in incontinence frequency. Finally, we will examine the attenuation of the estimated effect of treatment on incontinence frequency after controlling for changes in the proposed mediators, as an estimate of the proportion of the treatment effect explained. Confidence intervals for proportion of the treatment effect explained will be computed.[22]

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CHAPTER 3

STUDY ORGANIZATION AND POLICY

3.0 STUDY ORGANIZATION AND POLICY

3.1 OVERVIEW

The Program to Reduce Incontinence by Diet and Exercise (PRIDE) was initiated and designed by the investigators and consultants, who are committed to conducting the study in a uniform manner, adhering to the common protocol and Operations Manual and following standards of Good Clinical Practice. Standardization, supervision and coordination of all procedures will be enhanced through peer review and quality control mechanisms.

PRIDE includes two clinical centers, a Coordinating Center and the Sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases. Contact information for study personnel can be found on the password-protected PRIDE website at http://www.keeptrack.ucsf.edu/

3.2 PARTICIPATING UNITS

3.2.1 Clinical Centers

Two clinical centers are participating in this study:

The Miriam Hospital/Brown Medical School, Providence, RI
The University of Alabama, Birmingham, AB

The clinical centers are responsible for recruitment, randomization, delivering the weight loss intervention and the control group education program and for following a total of 330 study participants according to the study protocol and operations manual; transmitting data to the UCSF Data Management Group in a timely fashion with the lowest error rate attainable; addressing queries in a timely fashion, completing data forms and participating in the scientific aspects of the study including design, analysis, presentations and publications.

The Principal Investigator at each clinical center is responsible for the conduct of the study at his or her site and for gaining and maintaining local IRB approval in accordance with the principles of Good Clinical Practice.

3.2.2 UCSF Coordinating Center

The trial is coordinated at the Women's Health Clinical Research Center at the University of California, San Francisco. The Coordinating Center is responsible for coordinating the design and implementation of the study, analysis and dissemination of findings and for assuring the excellence of these processes. The Coordinating Center serves as the data and quality control center and oversees the communications and governance of the study.

3.2.3 National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)

The NIDDK is the sponsor of the study, which is administered through a UO1 grant. The NIDDK contracts independently with each functional unit through its respective institution and is responsible for administering the fiscal affairs of the study.

3.3 ADMINISTRATION

3.3.1 Steering Committee

The Steering Committee will be the primary governing body of the study and will be comprised of the Principal Investigators from the Clinical Centers, a behavioral consultant from the University of Arkansas, the Principal Investigator and Co-Principal Investigator of the Coordinating Center and project scientists from NIDDK. In the development stage of PRIDE, the Steering Committee will direct refinement of the study design, completion of the protocol, and development of interventions, operations manual and data collection forms. As recruitment and enrollment begin, the Steering Committee will monitor study progress and quality, and resolve issues that arise during follow-up. Finally, the Steering Committee will review and approve proposals for ancillary studies, analyses, scientific presentations and manuscripts. Publication Guidelines for PRIDE are attached as Appendix 3A.

The chairperson of the Steering Committee is the Principal Investigator of the Coordinating Center. The Committee generally meets by conference call, but will meet approximately annually in person.

3.3.2 Data & Safety Monitoring Board

The PRIDE Data and Safety Monitoring Board (DSMB) is comprised of five members with expertise in operational and biostatistical aspects of clinical trials, urinary incontinence and weight reduction. The DSMB convened at the end of protocol development to review the protocol and develop guidelines for DSMB activities and stopping rules. They will meet (either in person or by conference call) 6 months after recruitment begins, then approximately annually to review study progress, oversee participant safety, monitor data quality, and provide operational and technical advice to the Steering Committee and the NIDDK project officers. No member of the DSMB will participate in the study as an investigator or be involved in any way in the conduct of the study. The DSMB Guidelines and Stopping Rules are attached as Appendix 3B.

3.4 REGULATORY REQUIREMENTS

The following items should be kept on file at the clinical sites:

- IRB applications, renewals and approvals
- IRB Member List (alternatively a letter from the IRB referencing the institution's assurance number and the IRB chairman's name.)
- Informed Consent and annual renewals of IRB approval
- Site Staff CVs
- Research Team Signature List, including Staff ID#
- Site Visit Log
- Copies of Medical Licenses for Medical Staff
- Serious Adverse Event Reports
- Recruitment Advertisements

APPENDIX 3A

PRIDE PUBLICATION GUIDELINES

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PRIDE PUBLICATIONS GUIDELINES

A. PUBLICATIONS COMMITTEE

1. Mission

The mission of the PRIDE Publications Committee (PC) is to assure that data collected in the PRIDE trial result in high quality publications and presentations that clearly, accurately and completely convey the trial findings to the scientific community and the public. The process of application, review and approval for publications and presentations will be clear, fair, and uniform. Reviews and approvals will be accomplished in a timely fashion.

2. Objectives

- To encourage and facilitate high quality publications and presentations.
- To encourage broad participation by PRIDE investigators in publications and presentations
- To minimize overlapping publications and presentations
- To monitor (review?) publications and presentations of ancillary study data

3. Chair

Deborah Grady, MD, MPH is the Chair of the Publications Committee and will coordinate, monitor and review all proposals for presentations, publications, and press releases relating to the PRIDE trial. The chair will be responsible for:

- Organizing and chairing conference calls and meetings of the Committee;
- Leading a Publications Committee review and discussion of all publication/presentation proposals and assigning a primary reviewer from among members of the PRIDE PC;
- Supervising a tracking system that describes the status of all publication/presentation projects;
- Notifying the primary author that a proposal is approved or needs revision;
- Mediating disputes regarding publication/presentation content or authorship;
- Setting priorities for data analysis.

4. Members

The PRIDE Steering Committee will serve as the Publications Committee. Membership will be for the duration of the PRIDE trial. Members will:

- Define main and secondary manuscripts and presentations that should be prepared and encourage appropriate writing groups for these projects;
- Review proposals for publication and presentation;
- Review final drafts of publications before submission to a journal and review final presentation material before presentation;
- Act as primary reviewer on a subset of publication/presentation proposals as assigned by the PRIDE PC Chair;
- Participate in all conference calls and meetings of the PRIDE PC;
- Perform all work in a timely manner.

B. PUBLICATIONS

1. Types of Reports

- Main paper(s) report the between group findings for the primary endpoint(s);
- Secondary papers report the between group findings for the secondary endpoints;
- Trial-wide papers report findings based on data collected from all sites;
- Local papers report findings based on data collected from a subset of sites;
- Abstracts report any PRIDE findings in abstract form submitted to national or international meetings;
- Presentations are oral reports of PRIDE findings made at national or international meetings;
- Press Releases announce any PRIDE findings to the media or the public.

2. Application and approval process for publication and presentation plans

a. Publication/presentation proposals

1. The primary author will submit a publication plan to the PRIDE PC for approval.

2. The publication/presentation plan should be submitted using the PRIDE Publications Review Form (Appendix 1) and contain the

following elements:

- The primary author/presenter and co-authors
- The research question
- A brief rationale describing the importance of the question
- The variables to be used in the analysis
  - predictor variable(s)
  - outcome variable(s)
  - potential confounding variable(s)
- A description of proposed analyses
- For publications – the intended journal and timeline for submission
- For presentations – the intended meeting, deadline for submission of abstracts, and meeting dates

3. The Chair of the Publications Committee may assign a primary reviewer for each proposal at least 2 weeks before the PRIDE Publications Committee is scheduled to review the proposal.

4. A Conference call or meeting will be held to review all proposals. The primary reviewer will lead the discussion of the proposed plan. Approval of 2/3 of the committee will be required for approval.

5. The Chair will notify the proposer of approval and make sure that he/she is aware that the PRIDE PC must also review and approve the final draft before submission of a manuscript to a journal or an abstract for a meeting. If a proposal is not approved, the Chair will forward the written summary of the findings of the committee and suggested revisions to the lead author. The lead author may revise and resubmit the proposal.

b. Criteria for review of proposed PRIDE publications/presentations

The primary reviewer will prepare a brief critique of the assigned proposal that includes the elements described below. These criteria will also be used by the PRIDE PC to determine the merit of proposed publications and presentations.

- scientific merit of the research question
- appropriateness of the study design
- appropriateness of data analysis plans
- appropriateness of data presentation plans

- availability of data in PRIDE to complete the planned analyses and presentations
- expertise of the writing group
- number of approved or pending publication/presentation requests for the lead author and co-authors

c. Applications for similar analyses

If more than one application for similar analyses is received, the Chair will request that the investigators resolve the overlap or submit a joint proposal. If irreconcilable differences exist, the PC will independently evaluate the publication requests and assign the publication to one of the writing groups.

3. Authorship

a. Authorship eligibility

Authors must be a member of the Steering Committee, an investigator at a clinical site or an investigator of an approved ancillary study who has worked on the PRIDE trial. Other persons associated with the trial (such as clinic coordinators, fellows, research assistants, etc.) may be approved as authors on a case-by-case basis by the PRIDE PC.

b. Authorship responsibilities

All authors must participate in the writing of the paper or abstract in accordance with the International Committee of Medical Journal Editors Guidelines (N Engl J Med 1991;324:424-8).

c. Lead author

The lead author plays a key role in PRIDE publications and presentations. The lead author of the PRIDE main paper and secondary papers will be decided by the Steering Committee. For other papers, the investigator who first conceived of the project and submitted a plan to the Publications Committee will have the option of serving as lead author. If a writing group conceives of a project, the group may choose the lead author. The lead author will be responsible for all communication with the PRIDE PC, will choose co-authors and will be responsible for the quality and content of

the manuscript or presentation. Conflicts concerning who is the lead author should be resolved by all members of the writing group. If a group is unable to resolve a conflict, the PRIDE PC will adjudicate and assign lead authorship.

d. Co-authors

Co-authors will generally be limited to five (plus the lead author). Reports of the primary and secondary results of the study may include a larger author group. Co-authors may volunteer for projects, with conflicts worked out by the lead author with assistance of PC if necessary. Co-authors should be listed in order of contribution, as established by the lead author, except that the senior author may be listed last if preferred. All co-authors must participate substantively in the analysis and writing and review and approve the final version, in accordance with the International Committee of Medical Journal Editors Guidelines.

e. PRIDE Acknowledgments

All main, secondary and trial-wide papers, abstracts and presentations should include the PRIDE trial in the title and/or the PRIDE study research group in the authorship line.

4. Manuscripts

Approval of PRIDE manuscripts by the PRIDE PC will occur as follows:

- The draft for initial submission to a journal should be submitted to the Chair of the PC who will distribute it to all members of the PRIDE PC;
- Members of the PC will indicate their approval or disapproval and suggested revisions within 10 working days from the fax or electronic transfer date or 14 working days from the mailing date of the paper. Failure to respond to request for approval within the time limit will be taken as approval of the paper. Approval of 2/3 of the committee will be required for approval to submit the draft;
- The revised draft should be reviewed once more by the Committee or an appointee;
- Published papers will be archived at the PRIDE Coordinating Center.

5. Abstracts and presentations

- All abstracts and presentations describing PRIDE trial-wide findings must be approved by the Publications Committee prior to submission or presentation.
- Deadlines: Drafts of abstracts and outlines of presentations (including the findings and conclusions) must be received by the Publications Committee Chair at least 20 working days before the abstract deadline or date of presentation. The Chair will send materials to members of the Publications Committee, who will indicate their approval or disapproval and suggested revisions within 10 working days from receipt of the abstract or presentation. Failure to respond to request for approval within the time limit will be taken as approval. Authors and presenters will be notified about approval and recommended changes within 20 working days of receipt.
- Based on unanimous vote, the PRIDE PC may require that an abstract be withdrawn from submission.
- Hard copies of slides or posters should be sent to the Publications Committee for review and approval prior to presentation.

6. Press Releases

- All press releases describing PRIDE trial-wide findings must be approved by the Publications Committee prior to submission or presentation;
- Drafts of press releases (including text and presentation material) must be received by the Publications Committee Chair at least 20 working days before the date of presentation. The Chair will send materials to members of the Publications Committee and the Berlex Public Relations department who will indicate their approval or disapproval and suggested revisions within 10 working days from receipt of the press release. Failure to respond to request for approval within the time limit will be taken as approval. Authors and presenters will be notified about approval and recommended changes within 20 working days of receipt;
- Based on unanimous vote, the PRIDE PC may require that a press release be withdrawn from submission.

C. MISCELLANEOUS

- If the Publications Committee has not received a draft of an abstract, presentation, or manuscript within one year after approval of the plan

(assuming that data are available for analysis), approval for the plan will be withdrawn and the project may be completed by another writing group;

- When proposals for publications/presentations include members of the PRIDE PC committee as a lead or co-author, the committee member will not take part in the review or discussion of the proposal and will not vote on approval.

D. APPENDICES

1. Form for submitting publication/presentation plans
2. Guidelines for Reviewers and Format for Primary Review

PRIDE PUBLICATIONS GUIDELINES
APPENDIX 1
Format for PRIDE Publications/Presentation Proposals

Please use this outline to submit publication and presentation plans for approval by the PRIDE Publications Committee. All requested information must be complete before the proposal will be sent to the committee for review.

1. Date of Submission
2. Primary Author/Presenter:
   Name, Title
   PRIDE Affiliation
   University/Agency
   Department
   Mailing Address
   Fax:
   Phone:
   E Mail:
3. Co-authors:
   Name, Title
   PRIDE Affiliation
   University/Agency
   Department
4. Title of publication/presentation
5. Type of paper (i.e. main paper, secondary paper, presentation, etc.)
6. Research question
7. Brief rational describing the importance of the question
8. Variables to be used in the analysis
   - predictor variable(s)
   - outcome variable(s)
   - potential confounding variable(s)
9. Description of all proposed analyses
10. For publications: the intended journal and timeline for submission
    For presentations: the intended meeting, deadline for submission of abstracts and meeting dates.

PRIDE PUBLICATIONS GUIDELINES
APPENDIX 2
Format for Primary Review

1. Title of publication/presentation
2. Scientific merit of the research question
3. Appropriateness of
   - study design
   - data analysis plans
   - data presentation plans
4. Is data in PRIDE available to complete the planned analyses and presentations?
5. Does the writing group have appropriate expertise?

APPENDIX 3B

DATA AND SAFETY MONITORING BOARD GUIDELINES
PROGRAM TO REDUCE INCONTINCE BY DIET AND EXERCISE

The Program to Reduce Incontinence by Diet and Exercise (PRIDE) was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to determine if weight loss results in improvement in urinary incontinence among overweight and obese women with incontinence.

The progress of PRIDE and the study's potential to attain its goals will be regularly evaluated by an independent Data and Safety Monitoring Board (DSMB). This committee will periodically review the conduct and outcomes of the study and provide feedback to the NIDDK and PRIDE Investigators on the overall performance of the study with particular attention to protecting the safety of PRIDE participants.

The DSMB will consist of individuals who are independent of the institutions and investigators participating in the trial and who have no financial ties to the outcome of the trial.

A. RESPONSIBILITIES OF THE DSMB

Prior to implementation of the trial, the DSMB will evaluate the study design, review informed consent documents and plans for recruitment, adherence, interventions, data quality and safety monitoring.
At periodic intervals during the course of the trial, the responsibilities of the DSMB are to:

- evaluate the progress of the study, including adequacy and timeliness of participant recruitment, adherence to the visit and interventions protocols, data quality and timeliness, efficacy of the intervention to produce and maintain weight loss, effects of weight loss on frequency of incontinence, participant safety, and other factors that can affect study outcome;
- consider factors external to the study when relevant information, such as scientific or therapeutic developments, may have an impact on the safety of the participants or the ethical conduct of the trial;
- ensure data integrity;
- conduct interim analyses in accordance with stopping rules that are

clearly defined in advance of data analysis;
- ensure confidentiality of data and the results of monitoring;
- report to the NIDDK and PRIDE Investigators on the scientific progress of the trial and the safety of participants;
- make recommendations to the NIDDK, PRIDE Investigators and Institutional Review Boards on continuation, termination, or other modifications of the trial.

B. MEMBERSHIP

The members of the DSMB are appointed by the NIDDK. The DSMB is comprised of individuals who are experts in urinary incontinence, weight loss, epidemiology and biostatistics. The NIDDK Project Scientist serves as Executive Secretary. No member of the DSMB should participate in the study as an investigator or be involved in any way in the conduct of the study, and no member may have any financial interest in the results of the study. Fiscal support for DSMB members from makers of weight loss products or treatments for urinary incontinence must be disclosed to the PRIDE Steering Committee, and the possibility of conflict of interest will be considered on a case-by-case basis. PRIDE DSMB members are listed in Appendix I.

C. DSMB PROCESS

The DSMB will meet periodically by conference call and in person. Agendas for the meetings will be developed by the DSMB Chair and Executive Secretary with support from the Coordinating Center. An outline of proposed meetings is provided in Appendix III.

The first meeting should take place before initiation of the trial to discuss the protocol, interventions, and safety measures and to establish guidelines for monitoring.

Following the initial meeting, the DSMB should meet at least yearly to review accumulated data on adequacy and timeliness of participant recruitment, adherence to the visit and interventions protocols, data quality and timeliness, efficacy of the intervention to produce and maintain weight loss, effects of weight loss on frequency of incontinence, participant safety, and other factors that can affect study outcome. The initial meeting and meetings during which interim analyses are presented should be in person, but other meetings may be conducted by conference call (Appendix III). An emergency meeting of the DSMB may be called at any time by the Chair or NIDDK should questions of participant safety

arise.

DSMB meetings will consist of an open and a closed session. The *open sessions* may be attended by investigators and NIDDK staff, and should always include the principal investigator and the study biostatistician. Issues discussed at open sessions will include conduct and progress of the study, recruitment, adherence with the visit and interventions protocols, data quality and timeliness, problems encountered and aggregate outcome data. Participant-specific data and treatment group data will not be presented in the open session.

The *closed session* will be attended only by voting DSMB members and appropriate NIDDK staff representative(s), but others may attend if requested by the DSMB. A representative from the UCSF Coordinating Center will attend all closed sessions to present outcome data and answer questions about data format and derivation, but will not be a voting member. Between groups comparisons of all safety and efficacy variables will be presented at the closed session. All discussion at the closed session is completely confidential.
If requested by the DSMB, the closed meeting may be followed by an *executive session* which will include only voting DSMB members.
Should the DSMB decide to issue a recommendation to terminate or alter the study protocol, a full vote of the DSMB will be required. In the event of a split vote, a simple majority vote will rule and a minority report should be appended.
The DSMB will review the protocol of approved and funded studies ancillary to PRIDE, but will not review the conduct and outcomes of these studies.

D. REPORTS TO THE DSMB AND RECOMMENDATIONS OF THE DSMB

1. Interim DSMB Reports

Interim reports are prepared by the PRIDE Coordinating Center and distributed to the DSMB members at least 5 days prior to a scheduled meeting. The interim reports will be numbered and provided in sealed envelopes within an express mailing package to maintain confidentiality. The contents and format of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB. Interim data reports generally consist of two parts:

Open Session Report - provides information on recruitment and projected completion dates, adherence to the visit and interventions protocol, quality and timeliness of data, baseline characteristics, and other general information

on study status. The Open Report will also contain data on study drop-outs by group, including number, reason, and baseline characteristics. Open reports will include aggregate outcome data on changes in weight that occur during the weight loss intervention, but no data on changes in weight during the weight maintenance intervention or changes in frequency of incontinence.

Closed Session Report - contains data on study progress and outcomes between treatment groups, including changes in weight and frequency of incontinence, serious adverse events and safety. The Closed Session Report is confidential. Data files to be used for interim analyses will have undergone established editing procedures to the extent possible, but all data, both edited and unedited will be used to prepare interim reports. Interim analyses of outcome data will be performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined (Appendix II).

Copies distributed prior to and during a meeting will be collected by the Coordinating Center following the meeting. One copy will be retained in a locked, confidential file at the Coordinating Center and all others will be shredded.

2. DSMB Recommendations

The DSMB Chair will prepare minutes of the open and closed sessions, including any recommendations for changes in the PRIDE protocol, that will be approved by the Board and sent to NIDDK. The NIDDK Project Scientist will distribute minutes of the open session to the PRIDE Principal Investigators within 4 weeks of each meeting.

The minutes of each DSMB closed session should conclude with a recommendation to continue, terminate or alter the study. A recommendation to terminate the study or alter the study protocol may be made by the DSMB at any time by majority vote. Such recommendations will be transmitted to the NIDDK and reviewed immediately. Recommendations of the DSMB that are accepted by the NIDDK will be transmitted by the Project Scientist to PRIDE Principal Investigators and business officials of the grantee institutions as rapidly as possible. In the event of a split vote in favor of continuation, a minority report should be included in the regular DSMB closed report. It is the responsibility of the Principal Investigators at each PRIDE site and the Coordinating Center to assure that DSMB recommendations are sent to co-investigators and to each IRB.

E. ACCESS TO INTERIM DATA

Access to the accumulating endpoint data should be limited to as small a group as possible. The PRIDE Coordinating Center will prepare mock DSMB Closed Reports, tables and analyses using dummy treatment assignment variables. Before each DSMB meeting, one statistician/programmer at the Coordinating Center will complete the Closed Report using the real treatment assignment variables. No other personnel at the Coordinating Center, NIDDK or clinical sites will have access to treatment assignment codes.

F. CONFIDENTIALITY

All closed materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

PRIDE DSMB GUIDELINES
APPENDIX 1
DATA AND SAFETY MONITORING BOARD MEMBERS

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PRIDE DSMB GUIDELINES
APPENDIX II
Rules for Altering or Stopping PRIDE

This section provides guidelines for altering the PRIDE protocol or stopping the study early. While statistical guidelines for stopping the study at one formal interim analysis (approximately March 1, 2006) are provided, multiple other considerations will guide the decisions of the DSMB.

A. MONITORING RECRUITMENT, RETENTION AND DATA QUALITY

PRIDE must achieve planned power and data quality to provide a valid and accurate answer to study questions. The adequacy of recruitment, retention and data quality by clinical site will be assessed by the DSMB early in the study to ensure that the study is achieving planned power and data quality.

1. Recruitment goals will be established by the PRIDE Steering Committee and Coordinating Center based on the assumption that participants will be randomized in blocks of approximately 84 every 5 months over the 24-month enrollment period. Enrollment lagging more than 2 months behind these goals will be of concern, and may trigger added evaluation, effort and approaches to recruitment. Enrollment lagging more than 4 months behind these goals will be of major concern, and may trigger changes in enrollment criteria, interventions or other aspects of the trial protocol.
2. Goals for retention in PRIDE will require that no more than 15% of participants discontinue attending PRIDE assessment visits. Retention less than 85% will be of concern, and may trigger added evaluation, effort and approaches to improve retention. Retention of less than 75% will be of major concern, and may trigger changes in visit structure, interventions or other aspects of the trial protocol.
3. Data quality will be assessed using measures such as time from study visit to data entry, time to resolution of data queries, number of missing forms, and proportion of all study variables queried. Guidelines for concern regarding these measures are outlined below:

Measure	Goal Value	Acceptable Value
• time from visit to data entry	< 2 week	< 3 weeks
• time to resolution of queries	< 2 week	< 3 weeks
• number of missing forms	0	<5%
• proportion of variables queried	5%	<10%

B. METHODS FOR INTERIM MONITORING OF WEIGHT LOSS, FREQUENCY OF URINARY INCONTINENCE AND SAFETY

1. Stopping or Altering PRIDE for Safety

The primary aim of PRIDE is to determine if modest weight loss results in improvement in urinary incontinence among obese and overweight women with incontinence. The weight loss intervention includes standard approaches to diet and behavioral change that have been used successfully in many prior studies. An important secondary aim is to determine if a motivation-based weight maintenance program results in improved weight maintenance compared to a skills-based weight maintenance program. This intervention is innovative for weight maintenance, but the elements of this motivation-based program have been used in other successful behavioral interventions. PRIDE investigators believe that both the weight loss and weight maintenance interventions are safe. Investigators will carefully track potential serious adverse events that will be reviewed at each DSMB in-person meeting or conference call. If evidence of serious harm emerges, the PRIDE DSMB may decide to alter or stop the study at any time for safety concerns.

2. Stopping or Altering PRIDE for Efficacy

PRIDE investigators expect that, compared to usual care, the weight loss intervention will result in an average of 6% weight loss (about 6 kg) over 6 months and that this change in weight will result in a reduction of about 6 episodes of incontinence per week. There is no scientific or ethical reason to stop or alter the study if this intervention proves to be more effective than expected.

The expected efficacy of the innovative weight maintenance program is less clear, but PRIDE investigators believe that participants randomized to the skills-based program will regain about 1/3 of the weight lost, while those in the motivation-based program will regain no weight. There is no scientific or ethical reason to stop or alter the study if this intervention proves to be more effective than expected.

Thus, as long as no safety issues arise, PRIDE will not be stopped or altered if the interventions are unexpectedly effective.

3. Stopping or Altering PRIDE for Futility

Answering the main PRIDE research question requires that the weight loss intervention result in greater weight loss in the intervention compared to the usual care group. Based on effects in prior trials, participants in the weight loss group are expected to lose 6% of their body weight (6 kg), compared to no loss in the usual care group. However, the effect of this degree of weight loss on frequency of incontinence is not clear, and is the main question in PRIDE.

If the 6-month weight loss intervention does not result in substantial weight loss, we cannot address the main PRIDE research questions. If no weight loss occurs, we cannot determine if weight loss leads to in improvement in urinary incontinence; similarly, if no weight loss occurs, we cannot determine if a motivation-based weight loss maintenance program is more effective than a skills-based program. Thus, if weight loss is less than expected in the weight loss group, the DSMB will give consideration to altering the intervention and to stopping the trial.

Stopping or altering PRIDE for futility will be based on estimates of the efficacy of the weight loss intervention at the point when approximately 75% of the participants have completed the program. Efficacy for weight loss will be assessed as the difference between the weight loss and usual care groups in change in weight from baseline to the end of the 6-month intervention period. Efficacy for improvement in incontinence will be assessed as the difference between the weight loss and usual care groups in change in number of incontinence episodes per week from baseline to the end of the 6-month intervention period. The analyses of these outcomes, as specified in the protocol, will use a random effects model for piece-wise linear mean trajectories for average weight and frequency of incontinence in the treatment and control groups. These analyses will not require alpha-spending.

At this interim analysis, consideration will be given to stopping the study for futility if the point estimate of the difference between the weight loss and standard care groups is not 4 kg or greater. The DSMB might consider continuing the study even if efficacy for weight loss is low *if* the intervention has resulted in an improvement in incontinence of at least 20% or greater. In this case, changes in dietary composition or exercise habits might be responsible for an improvement in incontinence.

C. OTHER CONSIDERATIONS

In addition to the statistical procedures described above, other important considerations will be weighed by the DSMB.

- Whether the results could be explained by possible differences between the groups in baseline variables;
- Whether the results could be explained by differences in retention or drop-outs between the groups;
- Whether the results are consistent among various subgroups of participants and across the centers involved in the study;
- Whether it is likely that the current trends in the data could be reversed if the trial were to be continued unmodified;
- The degree of additional precision or certainty in the results that could be obtained by continuing the trial; and,
- Whether there would be significant loss in external validity or credibility of the trial by change in protocol or discontinuation.

PRIDE DSMB GUIDELINES
APPENDIX III
DSMB MEETING SCHEDULE, MILESTONES AND GOALS*

Type†	Date	Milestones		Goals and Analyses
IP-1	05/1/04	Prior to initiation of the trial		Review protocol, interventions, and safety measures and establish guidelines for monitoring and stopping the trial.
CC-C	12/1/04	Early in recruitment		Evaluate recruitment.
IP-2	05/1/05	168 participants randomized 84 participants completed 3-mo visit 77 participants completed 6-mo visit	(50%) (25%) (25%)	Review and approve table formats for future conference calls and meetings. Evaluate recruitment, data quality, adherence to visit and intervention protocols.
CC-1	10/1/05	252 participants randomized 168 participants completed 3-mo visit 154 participants completed 6-mo visit 73 participants completed 12-mo visit	(75%) (50%) (50%) (25%)	Evaluate recruitment, data quality, adherence to visit and intervention protocols, efficacy of weight loss intervention and safety.
IP-3	03/01/06	336 participants randomized 252 participants completed 3-mo visit 231 participants completed 6-mo visit 146 participants completed 12-mo visit	(100%) (75%) (75%) (50%)	Evaluate recruitment, data quality, adherence to visit and intervention protocols, efficacy of weight loss intervention and safety. **Interim analysis of efficacy of intervention on weight loss and incontinence.**
CC-2	9/1/06	336 participants completed 3-mo visit 308 participants completed 6-mo visit 219 participants completed 12-mo visit 140 participants completed 18-mo visit	(100%) (100%) (75%) (50%)	Evaluate recruitment, data quality, adherence to visit and intervention protocols, efficacy of weight loss intervention, and safety.

* Assumes that randomization begins October 1, 2004, 336 participants are randomized in groups of 84 (providing 14 for each of 3 groups at the 2 clinical sites) every 5 months and that 56 participants will be lost to follow-up (17%), 28 (half) within the first 6 months, 16 additional by 12 months and 12 additional by 18 months.

† IP = DSMB in person meetings, CC-C = conference call with Chair and CC = conference call with DSMB.

Additional meetings, conference calls or meetings may be held if deemed necessary by the DSMB

CHAPTER 4

VISIT SCHEDULE

4.0 VISIT SCHEDULE

4.1 OVERVIEW

Candidates who are eligible for the study after completing the Eligibility interview may, at the clinic's discretion, be invited to an Orientation Visit. Further eligibility screening will be done at Orientation, Screening Visits 1 and 2 and at the Randomization Visit. When all eligibility criteria have been met the participant is randomized to one of two groups and followed for 18 months. Follow-up assessments are made during clinic visits at Months 6, 12 and 18.

4.2 VISIT MAP

The visit map (Appendix 4A) is a detailed list of the procedures and questionnaires that are to be administered at each of the study visits.

4.2.1 Visit Checklists

A visit checklist is provided as the first form of the package of data forms for each study visit. The checklist is used as a guide for site staff in conducting the visit and as a trigger for the Coordinating Center to expect data forms for that visit. All bubbles on the Visit Checklists will be data entered and queried with the exception of the Screening Checklist. Complete and fax the checklist at the end of each visit except for the Screening Checklist which should be faxed after SV2. Do <u>not</u> fax the checklist if the participant has missed the visit.

4.3 VISIT TIMELINE & VISIT WINDOWS

Recruitment and randomization for PRIDE are complicated by the need to form groups of participants that will stay together for motivational purposes for the duration of the trial. Eligibility assessment visits will be conducted individually, but the visits will be spaced to accumulate approximately 30 – 45 participants who will be randomized at about the same time and can attend intervention and education sessions in groups of about 10 - 15.

As of October 28, 2004, the maximum allowed interval between the Eligibility Screening interview and the randomization visit has been extended to 9 months. There will be no restrictions on the intervals between the Eligibility Screening, OV, SV1, SV2 and RV. These changes facilitate the accumulation of groups for intervention sessions.

Visit windows provide an optimal timeframe for completing follow-up visits. Visit schedule compliance reports will be provided routinely to investigators and to the DSMB.

4.3.1 Orientation Visit

The Orientation Visit (OV) is optional and can take place any time after the Eligibility Screening interview and before Screening Visit 1. If informed consent is obtained during Orientation, the 2IQ and Demographics forms can be completed at the visit.

4.3.2 Screening Visits

Screening Visit 1 (SV1) is followed by Screening Visit 2 (SV2). These visits may take place at flexible intervals before the Randomization Visit to allow staff to accumulate adequate numbers of participants to form the intervention and usual care groups.

4.3.3 Randomization Visit

The Randomization Visit (RV) must be completed within 9 months of the Eligibility Screening interview. If a participant cannot complete the RV within 9 months of the Eligibility Screening interview she must be eliminated from the screening process, but may be re-screened with a new ID number at a later date. If the RV is performed more than 3 months after Screening Visit 1 certain eligibility criteria must be re-checked. Please refer to the Guidelines for Delayed Screening Schedules, Ch. 9, Appendix 9G.

4.3.4 Baseline Urodynamic Study

The initial urodynamic study visit (UDS) must take place after SV2 and before the RV.

4.3.5 Follow-up Visits at Months 6, 12, and 18

Target dates for the follow-up visits will be based on the individual's randomization date:

6-month visit: Target date is 26 weeks after RV; window is 24-28 weeks
12-month visit: Target date is 52 weeks after RV; window is 50-54 weeks

18-month visit: Target date is 78 weeks after RV; window is 76-80 weeks

4.3.6 6-Month UDS

6-month UDS: Target date is 26 weeks after RV; window is 24-28 weeks

APPENDIX 4A

PRIDE VISIT MAP

STUDY EVALUATIONS/PROCEDURES	OV	SV1	SV2	Screening	UDS Baseline	Baseline/ RV	6mo	UDS 6 month	12mo	18mo
Eligibility Screening Form (Prior to all visits)										
Explain Study/Describe study requirements	Y			Y						
Informed Consent & HIPPA Authorization	Y	Y								
Collect Detailed Contact Information				X						
2IQ	Y	Y								
Health History (Medical, surgical, gyn, incontinence)				X						
Height & Weight for BMI				X						
Vital Signs		X	Y			Y	X		X	X
Urine Dipstick Analysis		X	Y		Y			X		
Demographics				X						
Concurrent Medications				X			X		X	X
7-day voiding diary and data entry form				X		X	X		X	X
Inclusion/Exclusion/Randomization						X				
UI Symptoms Questionnaire						X	X		X	X
Food Frequency Questionnaire				X			X		X	X
Health & Activity Form (SF-36)				X			X		X	X
Paffenbarger Questionnaire				X			X		X	X
24 hour pad test						X	X		X	X
Weight & Abdominal Circumference						X	X		X	X
Motivation Questionnaires (Baseline & Follow-up are separate)						X	X		X	X
Cost Utility Questionnaires (Baseline & Follow-up are separate)				Y	Y		X			
Incontinence Impact Questionnaire (IIQ)				X			X		X	X
Urogenital Distress Inventory (UDI)				X			X		X	X
Bowel Habits						X	X		X	X
Sexual Function Questionnaire						X	X		X	X
Beck Depression Inventory				X			X		X	X
Sleep Questionnaires						X	X		X	X
Pelvic Muscle Exercise							X		X	X
Participant Satisfaction to change in UI							X		X	X
Serious Adverse Events (as needed)										
Termination Report (as needed)										
UDS Informed Consent & HIPPA (as needed)										
Pubococcoygues Strength (Brink's Test)					X			X		
Pelvic Organ Prolapse Quantification (POP-Q)					X			X		
Q-Tip Test					X			X		
Cough Stress Test					X			X		
NIF (Uroflowmetry)/Post-Void Residual (PVR)					X			X		
Cystometrogram (CMG/LPP)					X			X		

X = must be done at this visit; Y = can be done at either visit; X* = weight on

CHAPTER 5

TELEFORM GUIDELINES

5.0 TELEFORM GUIDELINES

PRIDE Study Forms are created with Cardiff Teleform software which allows the data to be faxed directly into the PRIDE database. Each page of each data form has a "banner" for information to identify the participant, the site, and the date of the visit or form completion.

5.1 PRINTING THE FORMS FROM THE WEBSITE

The PRIDE data forms are in PDF file packets and are organized by study visit. Forms can be printed as a visit packet or as an individual form. The Subject ID # and Acrostic can be entered once for an individual participant and then that information will be duplicated throughout the multi-page form or packet of forms.

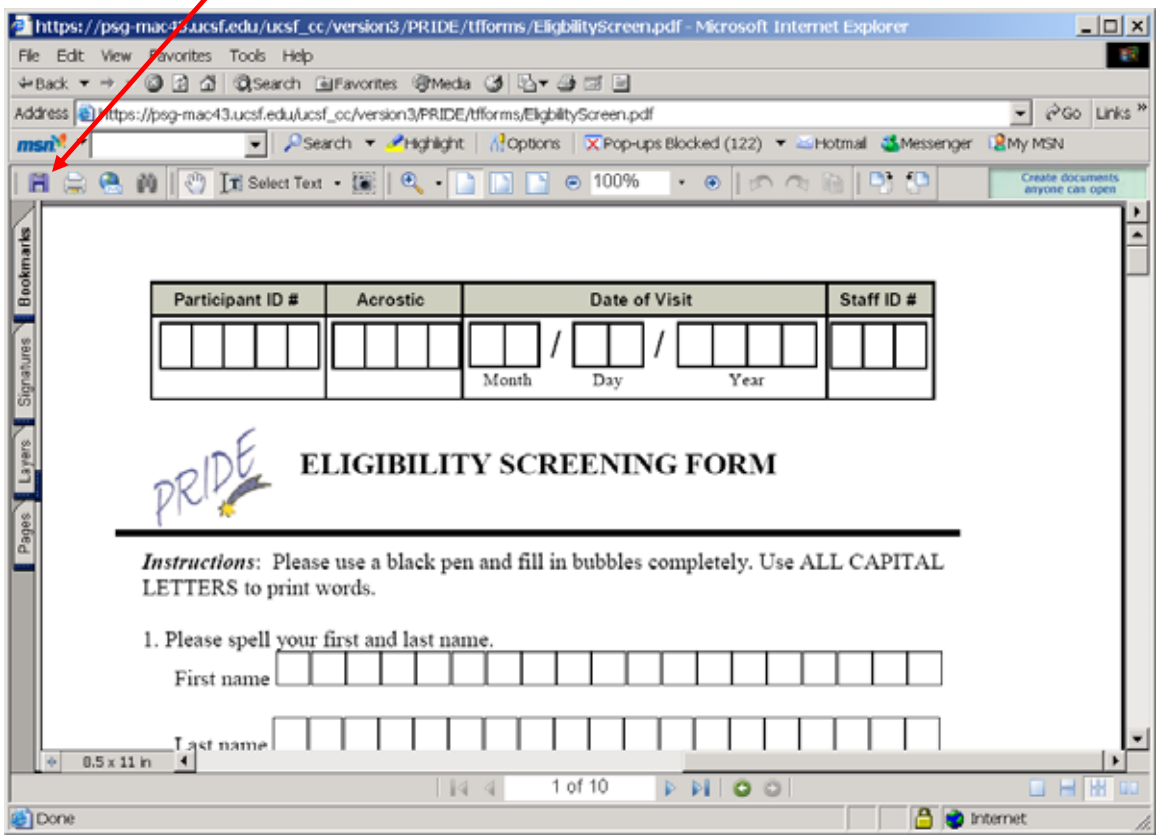
Step 1. Creating a folder to store forms on your hard drive.

We strongly recommend that you download the forms to your local hard drive and print from your computer. (This is helpful should there be interruptions in Internet service). To download forms, first create a folder on your hard drive to store the forms according to the following directions (for PC computers only, not Macintosh):

1. Double-click the 'My Computer' icon on the desktop of your computer.
2. Double-click the Local Disk (C):
3. Under the File menu, go to New, and then select Folder.
4. Name the new folder 'PRIDEForms'.
5. Close all the open windows.

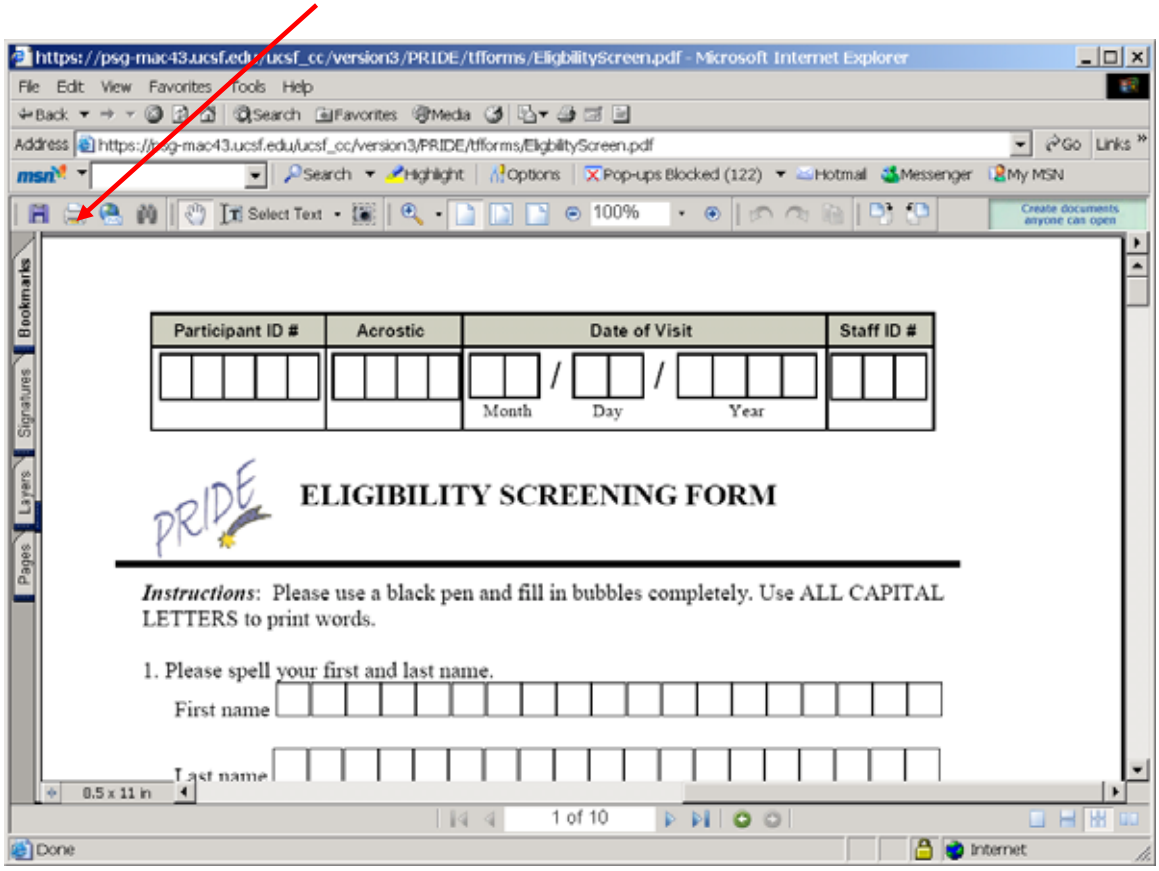
Step 2. Downloading the forms.

1. Go to www.keeptrack.ucsf.edu
2. Log onto the PRIDE website (see Chapter 19.3)
3. Click on the "Teleforms" link in the page header.
4. Click on the link for Eligibility Screening Form
5. Click the "save a copy" icon on the Acrobat menu (do NOT save from "file" menu above.)



6. When prompted, save the file to the folder that was created in Step 1 (C:\PRIDEForms).
7. Open each form individually and save it to the same folder.

NOTE: If want to print the forms directly from the website, be sure to use the PRINT icon in the Acrobat menu, not the PRINT icon in the Microsoft Explorer menu.



Step 3. Pre-filling Banner Information

You can pre-print as much or as little banner information as you want. For instance if you are doing a visit packet and you know that the banner dates will be different, please do not pre-fill these fields. However, please pre-fill as much as you can since typed letters and numbers are easier for teleform to recognize. If you want to skip a section, you can always place the cursor in the appropriate box and start from there.

- Don't forget to fill in the visit bubble manually. This is not a part of the pre-fill capabilities.
- PLEASE make the letters in the acrostic all caps.
- Staff ID should be completed by hand on each page after the page has been reviewed for missing or erroneous information, but it is possible to pre-fill this field as well.
- The Date of Visit *may* be pre-filled; however, be aware that this creates problems if the participant fails to appear or re-schedules at the last minute.

1. Open the form file from your hard drive (C:\PRIDEForms folder) in which you want to print banner information. Double click on the file, and it should open into Adobe Acrobat Reader.
2. Go to the first page of the form where the Subject ID #, Acrostic and the Date of Visit boxes appear.
3. Click in the first box of the Subject ID # and type in the first number.
4. Hit TAB, and type in the next number, then repeat this sequence until the cursor jumps to the Acrostic box.
5. Fill out the participant's Acrostic using ALL CAPITALS and TAB in between each letter until the cursor jumps to the Date of Visit.
6. Continue to fill in the Date information as described above.
7. Go to the File menu and Print.
8. Click 'OK'.
9. The form will print with the pre-filled information on every page.
10. Close the file. If prompted 'Do you want to save changes before closing,' select 'NO.'
11. Repeat **Steps 1-10** to print a form for another participant.

Note: To correct a mistake put your cursor in the erroneous box and simply type over.

5.2 FORMS COMPLETION: THE BASICS

A few basic rules facilitate accurate computer "reading" of the data form that is faxed from a clinical site.

a. Use a black ball-point pen. Do not use a felt tip pen that bleeds, a pencil nor any other color pen.
b. Avoid making any stray marks:
   - Don't mark or write in or around the four corners of the page.
   - Do not mark or punch holes on the form anchor boxes or on the form ID code box.
   - Don't make any extraneous notes on the form. Record notes only in designated areas.
c. Fill in the bubbles completely:
   - Stay within the lines
   - Don't use an "X" or a "√" in the bubbles
d. Do not fold, staple, or mutilate the data forms in any way that has not previously been approved by the Coordinating Center.

5.3 LETTERS AND NUMBERS

Please review the examples in Appendix 5A

a. Print in capital letters
b. Print only one letter or number per box
c. Keep the letter/number completely inside the box
d. Do NOT cross zeros (0), sevens (7) or 'Z.' The boxes are fields that are pre-defined in the data system. If the field has been defined as a number field it will read 0 as a number and not as the letter O.
e. Avoid "curly-cues" on letters and numbers.
f. Make your letters and numbers as similar as possible to the example in Appendix A.
g. Pay particular attention to the following groups of letters that are often difficult to distinguish from each other.
   P, D, O
   L, C,
   U, O

5.4 "COMMENTS"BOXES AND "PLEASE SPECIFY" FIELDS

Some of the forms contain boxes to write in, with instructions to provide "Comments," "Describe," or to "Specify." These fields should be filled in by printing in capital letters, one letter per box, and using a black pen. Please be as concise as possible, print clearly, and do not use cursive handwriting.

5.5 CORRECTING A MISTAKE

See Appendix 5.B for examples.

DOs:

- cross out the wrong answer by drawing a line through the mistake
- fill in the correct answer in the appropriate bubble if applicable or write the correct response beside the crossed out mistake
- circle the correct answer and initial and date the correction
- leave questions blank that the participant cannot or refuses to answer

DO NOTs:

- never attempt to erase pen marks
- never use correction tape/white out (i.e., Liquid Paper, etc.)

5.6 SCREENING ID & ACROSTIC

Each clinical site will have a set of screening numbers assigned to candidates. A unique screening identification number will be assigned to each candidate who has an Eligibility Screening interview, whether she is found eligible for the study or not.

The first digit of screening ID numbers for the Miriam Hospital is "1" and the first digit of the screening ID for the University of Alabama is "2", followed by 4 digits of sequential numbers.

The Screening ID Number Assignments

Miriam Hospital: Screening ID sequence from 10001 to 19999

University of Alabama: Screening ID sequence from 20001 to 29999

This screening ID number is coupled with an **acrostic of four letters**, **the first two letters of the participant's first name and the first two letters of her last name.** The ID number with acrostic will be used to identify the participant throughout the entire study and will be entered into the banner of every page of every data form, whether automatically generated from the data system when the forms are printed, or written on the form by hand.

Once the screening ID and acrostic have been sent to the Coordinating Center on the Eligibility Screening Form they are locked into the data system. The ID and acrostic on the first faxed page of the Eligibility Screening Form establishes a 'gold standard' ID and acrostic table. All forms with unmatched ID or acrostic will be rejected. You will have to contact the Coordinating Center to make any changes to these two fields, so be sure to check this entry very carefully.

5.7 STAFF ID NUMBER

Each site staff member must be assigned a Staff ID number composed of the Site identifier (Miriam = 1; UAB = 2) and a 2 digit staff number. The Staff ID number of the person completing the form must be entered in the banner of every page of every data form by hand. The Study Manager should keep a log sheet of staff ID's, assigning a unique number to every staff member and recording the dates they started and stopped working for the study.

5.8 DATES AND VISIT BUBBLES

Most data form banners include a date. Generally this is the date of the visit, or occasionally, the date the form is completed. The date must be filled in for every page of every data form, either electronically or manually. Specific instructions will be given in sections of the OM that describe the visits.

Visit bubbles appear under the title of each form unless the form must be completed at one specific visit. Only one visit bubble can be selected for each form.

5.9 FAXING THE FORMS

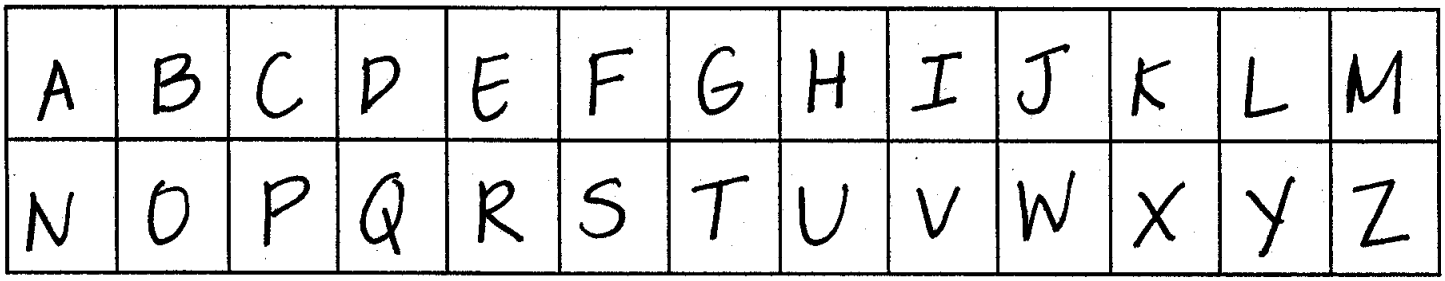
The study forms should be faxed to the UCSF DMG data system **(415-597-9174)** on the same day as the visit. The DMG will not receive any paper copies of the data forms.

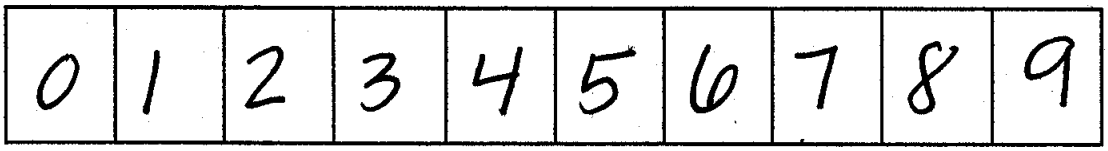
1. Always fax by feeding the tops of the forms into the fax machine.
2. Do NOT include a cover sheet.
3. Do NOT fax any examiner visit notes.
4. Do not fax "DO NOT FAX FORMS" as identified at the bottom of the page.
5. It is highly recommended that you maintain a fax log of all Teleforms for each study participant. Appendix 5C has an example of a recommended log that can be customized if you wish.

DATA FAX NUMBER: 415-597-9174

APPENDIX 5A

OPTIMAL NUMBERS AND LETTERS





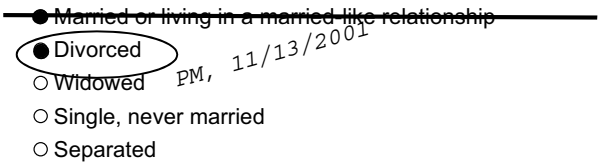
APPENDIX 5B

DATA CORRECTIONS

Example 1: Changing a response to a YES/NO or mutliple choice quesiton.

In this example, the participant marked incorrect marital status category. She is actually divorced but marked married by mistake.

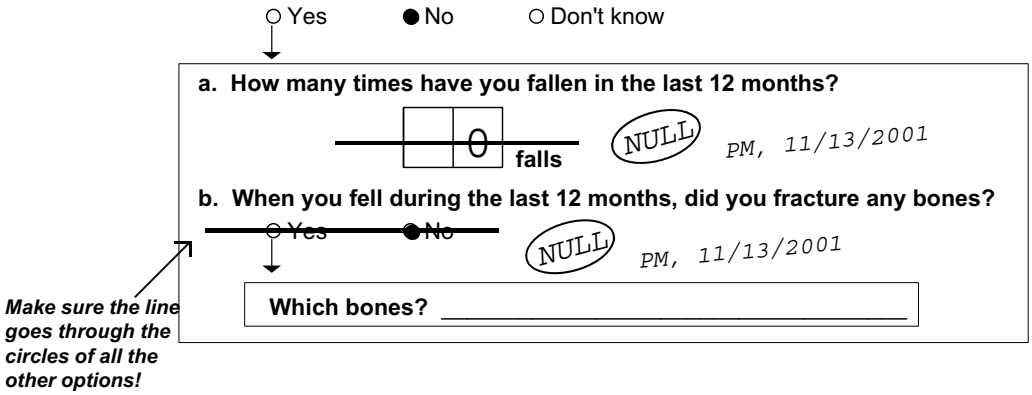
1 **What is your current marital status?**



Example 2: Changing a response to a YES/NO, mutliple choice or fill in the blank quesiton to null.

In this example, the participant marked answers to parts a and b when she was no supposed to. The answers to these questions should be blank, or null.

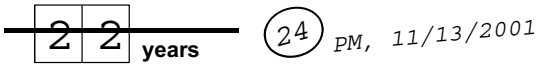
3 **In the last 12 months, have you fallen and landed on the floor or ground or fallen and hit an object like a table or chair?**



Example 3: Changing a response to a fill in the blank quesiton.

In this example, the participant wrote in 22 years when she meant to write in 24 years.

4 **How long have you been in this current living arrangement?**



Do NOT correct mistakes as the following:

APPENDIX 5C

SAMPLE FAX LOG

Fax Log for Subject ID: __ -__ __ __ __ Acrostic: __ __ __	Form Faxed **(please initial and date)**	Fax Confirmation Received **(please initial and date)**	Website Checked to confirm not missing **(please initial and date)**	Form Re-faxed, if applicable **(please initial and date, if necessary)**
Eligibility Screening Form				
2IQ				
Health History				
Height & Weight for BMI				
Vital Signs				
Urine Dipstick Analysis				
Demographics				
Medications				
7-day voiding diary data entry form				
UI Symptoms Questionnaire				
Food Frequency Questionnaire				
Health & Activity Form (SF-36)				
Paffenbarger Questionnaire				
24 hour pad test				
Weight & Abdominal Circumference				

Incontinence Impact Questionnaire (IIQ)				
Urogenital Distress Inventory (UDI)				
Bowel Habits				
Sexual Function Questionnaire				
Beck Depression Inventory				
Sleep Questionnaire				
Pubococcoygues Strength (Brink's Test)				
Pelvic Organ Prolapse Quantification (POP-Q)				
Q-Tip Test				
Cough Stress Test				
NIF (Uroflowmetry)/Post-Void Residual (PVR)				
Cystometrogram (CMG/LPP)				
Inclusion/Exclusion/Randomization				
Pelvic Muscle Exercise				
Participant Satisfaction to change in UI				
Serious Adverse Events (as needed)				
Termination Report (as needed)				

CHAPTER 6

RECRUITMENT

6.0 RECRUITMENT

6.1 RECRUITMENT POOL

The multi-component recruitment approach is site-specific but generally includes: (1) direct, community-based efforts using large media (newspaper notices, television ads, etc) and small media (brochures in local businesses, talks to local community, notices in churches, etc); (2) targeted mailings to potentially eligible women using available mailing lists and databases that will be purchased for this purpose; (3) direct recruitment from physician's offices (specifically in gynecology, primary care, and geriatric medicine); and (4) presentations at Grand Rounds and other local medical forums by the Principal Investigators. Every effort will be made to minimize obstacles to participation, for example, by providing participants with transportation or parking reimbursement and by offering a flexible assessment schedule. All methods and measures used will be culturally sensitive and all staff (including recruitment staff) will be provided with training in this regard. The Coordinating Center will provide centrally developed recruitment materials, and will monitor recruitment at each Clinical Center on a real-time basis, lead periodic conference calls about recruitment and retention, and send regular reports to the Steering Committee and the NIDDK.

It is expected that PRIDE participants will be recruited over a period of 27 months at each of the two clinic sites. About 45 participants will be randomized in close proximity to one another to facilitate the formation of the intervention and usual care groups. The sites will send out waves of recruitment mailings clinics to facilitate the cluster randomizations.

Recruitment is planned to start July 1st, 2004 and last until October 1, 2006. The responsibility of each clinical center is to enroll 165 participants during this period.

6.2 RECRUITMENT BROCHURE

A recruitment brochure has been developed for PRIDE to be used by both clinical centers in their mailings or presentations. The brochure includes a self-addressed, tear-off postcard that can be mailed back to the site inviting a telephone call from the staff. The text of the brochure must be approved by the institutional IRB before the brochure is used. The brochure will be printed after IRB approval is received.

6.2.1 Targeted Mass Mailings

Age eligible women who report obesity and urinary incontinence as health

issues can be identified through ALDATA, a commercial list broker that supplies name, address, age, sex, and race. The Department of Motor Vehicles is another source for mass mailing lists but these do not include specific health issues.

6.2.2 Community Promotion

Most clinical centers have identified organizations, agencies, group residences, etc. that may have potential participants. Both sites will place newspaper ads in local and university newspapers, mail letters to physicians and send notices to university employees.

6.3 PRIDE RECRUITMENT AD

The Coordinating Center will draft a newspaper recruitment advertisement. The text of this ad must be approved by the institutional IRB before it can be used.

6.4 COORDINATING CENTER ROLE IN RECRUITMENT

The Coordinating Center is responsible for developing and producing recruitment materials, for monitoring, fostering, and encouraging the recruitment effort and for providing accurate and timely information on the number of participants screened and randomized at each center.

6.4.1 Recruitment Reports

The Coordinating Center will generate recruitment reports and disseminate them to the clinical sites and to the Project Office. Periodically, the Coordinating Center will provide status reports about recruitment to the PRIDE DSMB.

CHAPTER 7

INTERVIEWING GUIDELINES

7.0 INTERVIEWING GUIDELINES

7.1 OVERVIEW

The interviewer plays a critical role in a research study, often being the first contact a participant has with the study personnel. The attitude, personality and skill of the interviewer can directly influence the participant's decision to enter the screening process and later, to remain in the study. The ultimate goal of the research interview is to obtain standardized, accurate and reliable data, often from multiple sites. The skill with which the interviewer conducts the interview helps to ensure this goal is met.

This chapter contains general guidelines and techniques for recruiting and interviewing study participants, specific suggestions for maximizing the success of the interview procedures and ideas for handling difficult interviews.

Please note: People who volunteer for research studies are "*participants*", not "*patients*".

7.2 GENERAL INTERVIEWING PRINCIPLES

- Speak clearly, distinctly and not too quickly.

- When calling to screen potential participants, identify yourself and the institution you represent immediately.

- Be polite, friendly (but not chummy), enthusiastic and positive regardless of how many times you've administered the interview. Exude warmth and energy to make the participant feel comfortable but remember to be professional.

- Be confident, but always treat the participant with respect, patience and appreciation. Always remember that the participant is a generous volunteer, is providing something we need and yet may not experience a direct benefit.

- Call participants by name using titles if possible (Mrs., Ms., etc.,) unless the participant suggests otherwise.

- Respect the confidentiality of the information you receive. Never discuss personal anecdotes about other participants.
- Know the study and the interview process in enough detail to be prepared to answer questions such as:

- "What is the study about?"
- "How will it benefit me to be involved?"
- "Where did you get my name?"
- "How long will the interview take?"
- "Whom else are you interviewing?"

The most effective answers are brief, direct, and truthful. A potential participant most often wants to confirm your identity and the legitimacy of your call, and is rarely interested in any in-depth details of the study. Be honest about the time commitments involved for the clinic visits. Participants should not come expecting to rush through everything so they can be on time to another appointment. If you don't know the answer to a particular question, don't guess. Offer to call back after you've consulted with a colleague or supervisor.

- Don't give medical advice other than to suggest a source of health information or health professionals if necessary.

- Be very familiar with the interview form; practice interviewing a colleague, friend or relative of the same age and gender as the study population. Understand the purpose and meaning of the data items on the forms. If you don't understand, ask your supervisor for clarification.

7.3 INTERVIEWING TECHNIQUES

7.3.1 Overcoming Resistance

Getting cooperation from persons who are initially reluctant is important because their experience may be different from those of persons who cooperate readily.

- Listen carefully to their reasons.

- Be accepting, patient, calm, and reassuring as you try to persuade them to cooperate. With interviewing experience comes assurance, and assurance helps overcome resistance. Attempt to assure the candidate that he or she will make a valuable contribution to the health of other people.

- Although you may try to persuade a reluctant candidate, you must

respect the wishes and privacy of persons who really do not want to be involved.

7.3.2 Manage the Interview

- Control and focus the interview without dominating. Studies have shown that a participant often remembers more about the interviewer and how the interview was conducted than about the topics covered during the interview.

- Your job is to get information, not to show how much you know. You convey the importance of the participant's responses by listening carefully and concentrating on the content of the interview.

- Be politely firm and businesslike; timidity signals lack of confidence. If you communicate insecurity or hesitancy to participants, some of them will assume a power position, others will feel sympathetic and assume a "mother" position. In either case, the participant's responses could be biased: the participant assuming the power position could distort strong opinions; the mothering participant could try to make the interviewer's job easier by answering obligingly.

7.3.3 Facilitate Honest, Unbiased Responses

- Take no personal stake in the content of the interview. Make sure your opinions and behavior neither add to nor subtract from the intention of any items on the forms. Take care not to influence the participant's response.

- Be understanding. Accept what the participant says without showing reactions of either approval or disapproval; participants must feel that their ideas are important, and that there are not right or wrong answers. The participant should never be made to feel inadequate.

- In general, do not attempt to interpret or explain the question. Maintain neutrality. If a participant does not seem to understand a question, repeat the question slowly and clearly. Give the participant time to think.
- Bias in interviewing can compromise data. Interviewers can introduce bias into survey results by interpreting answers, favoring one answer

over another, treating some questions as sensitive, reacting to liked or disliked participant characteristics, leading the participant or using positive or negative filler words. To avoid these potential sources of bias, interviewers must perfect both neutral delivery and neutral response.

- Participants can bias their responses by trying to answer questions when they simply don't know the answers, by tailoring answers to put themselves in a better light, by giving responses they think their friends would, or by providing answers they think the interviewer expects. The interviewer overcomes participant's emotional, unconscious bias tendencies by presenting questions at a regular pace and by maintaining neutrality.

7.3.4 Follow the Script

- Follow the prepared script; don't improvise. This is important for collecting data in a consistent way.

- Don't skip any questions unless instructed to do so. Don't assume you can enter an answer based on a previous response.

- Ask all questions in the same order and exactly as they are worded on the questionnaire. The questionnaires have been designed and tested for a specific purpose and work best the way they are organized.

- Review the instructions for each form regularly. Do not rely solely on memory for detailed instructions on form use.

- Be alert to any problems that occur more than once during administration of the questionnaire such as misinterpretations of the question or awkward flow leading to confusion. Discuss such problems immediately with a supervisor, not with the participant.

7.3.5 Probe to Elicit a Response

Appropriate probes should be used whenever the participant is hesitant in answering the questions or has given an answer that is irrelevant, incomplete or vague. Don't accept a "don't know" without probing at least once, but be sure to be non-directive.

- Use neutral probes that do not suggest answers. Two of the most effective and most neutral probes are (a) repeating the original question and (b) silence. Sometimes 15 seconds of silence will elicit an answer to the question.

- Examples of other neutral probes:
  - "How do you mean?"
  - "In what way?"
  - "Please give me an example" OR "For example?" OR "For instance?"
  - "Tell me more about that"
  - "I just want your impression." OR "I just want your opinion."
  - "What else can you tell me about that?"
  - "If you had to choose, which would you say?"

- **Avoid** leading probes such as these because they suggest answers:
  - "Do you mean…"
  - "Then you feel…"
  - "Do you mean X or Y"

Some neutral probes are better than others. Instead of "anything else?" which invites a participant to say "no," you'll find that "what else can you tell me about that?" is more likely to elicit answers. Instead of "why?" you'll find "I'd be interested in your reasons" accomplishes the same purpose and is less likely to be threatening.

7.4 CONDITIONS OF INTERVIEWING

- All interviewing should be done in privacy. You cannot expect the same answers when a person speaks in front of others as when they speak to you alone.

- When conducting an interview in person, both of you should be seated comfortably in a quiet location. Try to be in a position that will:
  - allow you to have easy eye contact with the participant
  - enable you to be heard without raising your voice
  - avoid light glaring in either the participant's or your eyes
  - permit you to write unobtrusively

7.5 DELIVERY

- Use a brisk, businesslike pace, but don't rush the participant or show impatience.

- Vary from your established pace on cues from the participant. If the participant shows frustration or lack of understanding, slow down. If the participant shows annoyance or jumps in with answers to anticipated questions, speed up.

- Do not indicate surprise, pleasure, approval, or disapproval of any answer by word or action. Do not smile, grimace, gasp, laugh, frown, agree, or disagree. Even a slight intake of breath or a raised eyebrow may indicate to a participant that you are reacting to an answer. Project smooth, gracious acceptance of information, no matter how outrageous the content.

- Make your delivery smooth, natural, and enthusiastic. Avoid sounding like a robot. Sound fresh for everyone. You may ask the same questions a dozen times in a day, but participants hear them only once in their interview.

7.6 INTERVIEWING CHALLENGES

At times you may confront some difficulties in interviewing. Some suggestions on how to handle special situations follow:

7.6.1 A participant with difficult hearing

- Sit close enough to the participant so that you do not have to shout. Make sure your face is clearly visible and not obscured by hair, glare, or shadows for participants who might rely on lip-reading.

- Slow down and speak in lower-pitched (more bass-pitched, not soft-spoken or high-pitched) tones. If you need to increase the volume, move closer to the participant rather than shouting. For some people the more you raise your voice, the more distorted the voice sounds and the harder you are to hear. The participant may also turn a "good" ear toward you. Take this cue to speak clearly and distinctly toward that side.

- If necessary, let the participant read the questions from a blank form

while you read the questions aloud.

7.6.2 A participant with limited vision

If the participant is so visually impaired that they cannot read the materials, read the materials to the participant.

7.6.3 A participant with difficulty understanding a question

- Take responsibility for making questions understandable. Do not make participants feel that it's their fault if they don't understand a question.

- Take away the burden of not remembering: participants shouldn't feel ashamed by lack of recall. If a participant doesn't remember a date, lead a discussion back through some prominent seasons or events, repeating the question as you go.

- If a participant does not understand a question, repeat the question clearly, slowly and without raising your voice, possibly changing the emphasis of the words or the tone of your voice. Repeat it twice if the participant has patience for it. After that, record whatever answer the participant offers and go on.

- Do not reword or explain the question. Encourage the participant to do the best they can. If they still do not understand, treat as missing data and move on.

7.6.4 A very talkative participant

- Frequently you will encounter a participant who wants to talk at much length about herself, or in a social manner, or a participant who is not able or willing to focus on the individual questions. While being accepting of the person and their needs, do not hesitate to interrupt the participant gently but firmly, saying something like, "I don't want to take up too much of your time, so let me ask you now: (repeat question)."

- In a face to face interview, it also helps to lose eye contact with the participant, look down at the interview instrument, then look up and say, "Perhaps you can tell me more about that when we are finished.

Now I'd like to ask you…," "Isn't that interesting. Now let me ask you this…," as a last resort, "Excuse me, but let's get back to the question: (repeat question)."

7.6.5 A participant who is unable to handle the interview

In a very few cases it will be apparent that the participant is not physically, intellectually, and/or emotionally capable of participating in the interview, although they have agreed to do so.

- Judgment to discontinue the interview should not be based on incorrect answers to any single or group of factual or other questions, but on a trend indicating gross cognitive incompetence, inability to comprehend the questions, inappropriate answers, or grossly contradictory answers. These would indicate the instrument will not obtain meaningful information about the participant and is probably a sever burden to the participant.

- A participant who is not oriented as to time, place, etc., yet can give good information about her life, can be included in the study.

7.6.6 A participant who has a strong objections to questions

- If the participant is angry, reluctant, or impatient about a single question or series of questions, respond in a non-defensive tone as though you have heard the objection before. Don't delay the interview any more than necessary; move on to the next question. If the participant pursues the objection, suggest that, although the researcher had a purpose in including the question in the interview, the participant doesn't have to answer the question.

- If a participant hesitates or refuses to answer, repeat the question. Say, "Let me go over that again. If you don't want to answer, that's your choice; but my instructions are to ask each of the questions." Add that the participant's feelings or opinions about the question are important. If the participant still refuses, accept the refusal graciously and go on to the next question.

7.6.7 A participant who is impatient with the length of the interview

- If a participant is anxious to finish the interview and says so, say "I need only a few more minutes of your time. Your answers are important to us, and we'd like to have all of them."

7.6.8 A participant who is overly curious about the research

- Be ready with standard replies for people who want to know more about the research or why a specific question is included. Do not get involved in long explanations of the project, the forms, the research methods, or the outcomes of the study. Be sure to use standard responses.

7.7 REPEATED CONTACT INTERVIEW

- When appropriate, keep contact notes on your conversations with participants for use by other research staff. Record participant information that another interviewer might reasonably be expected to know, such as number of children.

- Review contact notes before each new contact. Be careful when using comments recorded by another interviewer. There is a difference between "remembering" a participant and "talking about" a participant, which may be interpreted as a breach of confidentiality.

CHAPTER 8

ELIGIBILITY SCREENING

8.0 ELIGIBILITY SCREENING

8.1 OVERVIEW

The goal of eligibility screening is to identify female candidates with urinary incontinence who are overweight or obese, likely to adhere to and benefit from the weight loss intervention, agree to participate and may do so safely. The ELIGIBILITY SCREENING interview can take place over the telephone or in person.

8.2 STUDY POPULATION

PRIDE will recruit 330 participants from 2 clinical centers over two and a half years beginning in July 2004 and continuing through October 31, 2006. Each participant will be followed for 18 months.

8.3 SOURCE OF MEDICAL CARE

Having PRIDE staff participate in the medical care of study participants could lead to differential treatment of participants in the two arms of the study and affect the outcomes under investigation. Thus, each candidate must have a health care provider outside of PRIDE who will provide primary care. Any candidate with coronary heart disease must have a letter of approval from her health care provider before enrolling in PRIDE to ensure that she can safely engage in the diet and exercise program. If a candidate does not have a source of medical care outside of PRIDE, study staff should help the candidate identify a provider.

8.4 BACKGROUND INFORMATION

Each interviewer should read Chapter 1 of the Operations Manual (the study protocols) carefully, review Chapter 4 (Visit Schedule), Chapter 7 (Interviewing Guidelines) and this Chapter 8 prior to beginning screening. The interviewer should be very familiar with the Eligibility Screening form and the purpose of the study and be prepared to answer the respondent's questions.

8.5 PREPARATION FOR THE INTERVIEW

Forms/Materials Needed For This Interview:

- Eligibility Screening Form
- Participant Tracking Log
- BMI chart
- List of Exclusionary Medications
- List of local physicians who are willing to take referrals
- Blank paper for making notes if necessary. Please do not make notes on the data forms
- A calculator

Forms for the Eligibility Screening interview should be printed from the PRIDE website prior to making contact with the candidate. The data forms for the PRIDE study have been converted to PDF files for easy printing (See Chapter 5, Section 5.1 for instructions). Until you talk to a candidate you cannot be sure of the acrostic, therefore it may be most efficient to enter the ID number on the website (or print it on the data form manually) and fill in the rest of the banner information by hand after the interview.

8.5.1 Participant Tracking Log

Each clinical center should keep a log of all persons screened over the phone or in person. This will be referred to as the Participant Tracking Log. The Participant Tracking Log will be for clinic use and organization only, and will not be entered into the PRIDE database. This log should contain at least the following information: (1) ID number and Acrostic; (2) the candidate's name; (3) the date the candidate was assigned the ID number; (4) a re-screening number if necessary and (5) miscellaneous comments. The Participant Tracking Log links the name to the study ID. Thus, in order to insure confidentiality, PRIDE staff must keep the log locked in a secure place or stored in a password-protected computer file.

8.5.2 Screening ID and Acrostic

Each clinical site will have a set of screening numbers that may be assigned to candidates. A unique screening identification number will be assigned to each candidate who has an Eligibility Screening interview, whether she is found eligible for the study or not.
The first digit of screening ID numbers for the Miriam Hospital is "1" and the

first digit of the screening ID for the University of Alabama is "2", followed by 4 digits of sequential numbers.

The Screening ID Number assignments

Miriam Hospital: Screening ID sequence 10001 to 19999
University of Alabama: Screening ID sequence 20001 to 29999

The screening ID number is coupled with an **acrostic of four letters**, **the first two letters of the participant's first name and the first two letters of her last name.** The acrostic letters should always be upper case. The ID number with acrostic will be used to identify the participant throughout the entire study and will be entered on the banner of every page of every data form, whether automatically generated from the data system when the forms are printed, or, printed by hand.

Once the screening ID and acrostic have been sent to the Coordinating Center on the Eligibility Screening Form they are permanently entered into the data system. The ID and acrostic on the first faxed page (page 2) of the Eligibility Screening Form establishes the ID and acrostic table. This is known as the "gold standard". All subsequent forms with unmatched ID or acrostic will be rejected. You will have to contact the Coordinating Center to make any changes to these two fields, so be sure to check this entry very carefully.

8.6 PURPOSE OF THE INTERVIEW

The initial, screening interview is the candidate's first personal contact with the clinical center. The purposes of the initial screening contact are to:

- Provide information to those who are interested in the study
- Pre-screen potential candidates
- Schedule an orientation or screening visit

The essential components of the initial interview are to:

- Provide a brief description of the study (refer to the protocol)
- Determine if the woman is interested in participating
- Obtain basic demographic information
- Ascertain basic eligibility for the study by gathering certain inclusion and exclusion information

- Encourage and schedule an Orientation Visit appointment for those who are eligible

The remainder of this chapter reviews each question on the ELIGIBILITY SCREENING FORM and describes how to code responses. If, at any point, the interviewer is unsure about how to answer a question or code a response, or about the eligibility status of the candidate, she should make an appointment to call the candidate back and then discuss the issue with a supervisor, the Principal Investigator or the Coordinating Center staff.

8.7 THE ELIGIBILITY SCREENING INTERVIEW

Generally, candidates for the study will call in response to an ad or mailing, or, the interviewer will be returning a message from an interested candidate. The interviewer should begin by stating her name and the name of the site. After briefly describing the study and answering questions, the interviewer should ask the candidate if she would be interested in participating. If she is not interested in participating, thank her for her time. Remind her to call back if she changes her mind or offer to call her back at a specified time. A sample introductory script is provided in Appendix 8A.
The investigator may choose to avoid screening women who have participated in intensive weight loss programs at her/his clinical site within the past 5 years since the intervention materials will be too similar. Please document the number of candidates who are not suitable study candidates due to previous participation in local intensive weight loss programs and provide these numbers to the Coordinating Center at the end of enrollment.

Investigators may also choose to avoid screening women who have clearly diagnosed health problems as described in questions 16 and 17 of the Health History form. An annotated version of these questions is available on the PRIDE website under "Study Documents, Miscellaneous."

8.7.1 Questions 1 – 3

These questions capture contact information and are for clinic use only. This page should NOT be faxed to the Coordinating Center as the candidate's name must be kept confidential. We recommend that you keep additional contact information (such as name of spouse, relative etc.) to facilitate follow-up.

8.7.2 Question 4

Confirm that the candidate is female. Do not rely on names or voices to identify gender. Males are not eligible.

8.7.3 Question 5 and Question 6

Establishes ethnicity. All ethnic/racial groups are eligible for the study. If the candidate refuses to answer the question or isn't sure of her ethnicity or racial group mark the category "Don't Know".

8.7.4 Question 7

Enter the candidate's current age. She must be 30 years of age or older, with no upper limit of age. If she is less than 30 years of age but will be 30 within the recruitment period, you may invite her to call back at that time. If she calls back she should be assigned a new ID number that should be entered in the appropriate column on the Participant Tracking Log. The reason she is being re-screened should be noted on the tracking log in the Comments section.

8.7.5 Question 8

Women who are pregnant or have been pregnant in the past 6 months are not eligible. Women who were pregnant or gave birth within the past 6 months may be invited to call back when the 6-month point is passed. If she calls back she should be assigned a new ID number that should be entered in the appropriate column on the Participant Tracking Log. The reason she is being re-screened should be noted on the tracking log in the Comments section.

8.7.6 Question 9

Record the candidate's height, generally given to you in feet and inches. Use your calculator to convert height to inches by multiplying the number of feet by 12 and then adding the inches (e.g. 5ft 4in is 5x12 +4 = 64 inches). If the candidate reports her height in meters, record that number in the appropriate box.

8.7.7 Question 10

Record the candidate's weight in pounds or in kilograms depending on which

she reports. If the weight was reported in kilograms use your calculator to convert to lbs: kgms x 2.2 = lbs and enter the weight in lbs also. If the woman says she doesn't know her weight, ask her if she can weigh herself quickly and conveniently. If possible, record this weight. If she doesn't have a home scale, ask her to make her best guess.

8.7.8 Question 10a

Using the height from question 9 and weight from question 10, refer to the BMI chart to find the candidate's Body Mass Index. You can use the "inches/lbs" chart or the "meters/kgms" chart. The BMI reading from either chart can be entered directly in 10a. If the BMI is 25 to 50 kg/m2 the candidate is eligible to continue the screening process. If the BMI lies outside this range she is not eligible and you should skip to question 30.

8.7.9 Question 11

Record the candidate's weight 3 months ago. If she doesn't remember, ask her if her weight has changed in the past three months (you can suggest she think about some life events that might have taken place 3 months ago that could help her recall). Ask the candidate to estimate as closely as possible her weight three months ago.

Note: If the weight is reported in kilograms use your calculator to convert to lbs: kgms x 2.2 = lbs. Enter the weight in lbs.

8.7.10 Question 11a

Use your calculator: enter the weight in question 10 (in lbs) and then subtract the weight in question 11 and enter the result in the box in 11a. **Mark whether the change is plus or minus.** If the result is a loss of 10 lbs or more, the candidate is not eligible at this time and you should skip to question 30. If there has been no change in weight enter 0 in box 11a. Candidates may be rescreened at a later time when weight becomes stable.

8.7.11 Question 12

It is important that the response to this question relates to the candidate's current experience of urinary leaking or dribbling. If she is not currently experiencing these symptoms, she is not eligible, and you should skip to

question 30. If the candidate answers "yes", then fill in the bubble and go to question 12a.

8.7.12 Question 12a

If the candidate has been leaking urine for less than 3 months she is not eligible; skip to question 30. The candidate may have trouble remembering when her incontinence began. You can help her recall by asking her to think of other dates or events that coincided with the onset of her incontinence.

8.7.13 Question 13

This is the most important qualifying criterion for PRIDE. The response should reflect the number of incontinent episodes per week that the candidate is experiencing on average. For most women, this number will be an estimate. Although the daily patterns of urinary incontinence (UI) may vary, the candidate must have at least 7 episodes per week to continue being screened*.

It may help to try to clarify the number of incontinence episodes based on the candidate's most recent experience – for instance, in the past week or month. Or, you may be able to help candidates with their estimates by suggesting they think about yesterday, then the day before yesterday, etc. For some candidates, it may help to think in terms of daily episodes, and multiply by 7.

Other ways to help the candidate think about types of episodes are by probing: "How often do you notice your panties (or protective pad) are wet?" or "Do you lose urine even slightly with a cough or when your are on your way to the toilet?" Remember, all incontinent episodes count, even dribbling on the way to the toilet or after completing a void, or small volume losses with a cough, sneeze, or lifting.

Typical Scenarios:

1. Some women may experience erratic patterns of UI, for example, having 6 episodes one day and none for the next three days. Women with stress UI may only leak with certain types of activity, or when their allergies are acting up and they are sneezing a lot. Even with urge UI they can have "good days" and "bad days". All these situations are acceptable as long as the total number of episodes per week adds up to 7 or more.

2. At this initial contact, some women may be embarrassed to report just how much leakage they are experiencing. If you sense that they are reluctant to answer this question you could say "A lot of women have trouble with bladder control, particularly as they get older. That is why we are doing this study" or "Accidental urine loss is a much more common problem than most women realize, since many are reluctant to discuss it. We're doing this study because it's so important to find ways to solve the problem." Try to make the candidate feel comfortable with any disclosure she makes and let her know she is not alone, that many women experience these symptoms.

3. In order to encourage the candidate to be forthcoming, you may tell her that, in order to participate in the study, she must have several episodes of leakage per week and that only a couple of times per week wouldn't be enough. However, you cannot tell her specifically the number of episodes that qualifies her for the study. Ask her to be as accurate as possible and help with her estimation as described above.

4. If the candidate reports having sneezed three times in close succession and lost urine each time, then these would be three episodes. If she reports losing urine constantly while running and notes the sensation of needing to urinate (urgency), then this is probably one episode of urge incontinence. To clarify, ask "Did you feel a sense of urgency or like you needed to urinate?"

5. In very obese women, the sensation of loss may be too subtle to notice at the time of the leakage, especially when they are wearing a bulky pad. You could probe by saying "How often do you have to change your pad? Is it usually soaked through?" In some obese women the urine that is leaked gets caught in folds of flesh and the woman doesn't realize she has leaked until she gets up and is wet. Some women may leak continuously due to an anatomical problem in the pelvic region. **If a woman cannot determine discrete episodes of leakage she will not be able to participate.** Thus a report of "continuous leakage" or "always being damp" excludes the candidate. The number of UI episodes is our primary outcome measure in PRIDE; participants must be able to tell when and how often they leak in order for us to measure change.

6. If the candidate has less than the minimum number of episodes (7) required to continue screening, but has trouble recounting the episodes, you could suggest that she keep track of her incontinence episodes for a few days by

recording them on her own calendar. You could continue the interview and, if she is eligible by all other criteria, arrange to call her back in a few days to complete Question 13. Women may tend to discount "dribbles" or underestimate the number of times they leak urine. The calendar will give her a better idea of the extent of her urinary incontinence and may encourage her to participate if she qualifies.

7. If the candidate experiences urinary leakage but doesn't have the required number of episodes per week you should use your own judgment about whether or not to re-screen her after 6 months to a year. If she seems to be an accurate reporter, appears to be eligible otherwise and is interested in participating, then a call back at a later date may be worthwhile. It is possible that her incontinence may worsen in the interim.

***The official study Voiding Diary completed between Screening Visits 1 and 2 will be the definitive measure of frequency of incontinence for eligibility purposes. Please note that, for enrollment in PRIDE, women must have 10 or more episodes of urinary incontinence documented on the first 7-day voiding diary. For general screening purposes this number has been reduced to 7 or more since many women will underestimate the number of times they leak or dribble until they keep a diary.**

8.7.14 Question 14

Urinary tract infections usually cause enough discomfort to cause a woman to seek medical help. If the candidate says she doesn't know, ask if she went to the doctor four or more times in the past year for a burning sensation when she urinated. If yes, she is not eligible; skip to question 30. If she doesn't know, then mark no, and continue to question 15.

8.7.15 Question 15

Any responses to this question allow for continued screening. However, if the candidate has been told that she has an active urinary tract infection (UTI), tell her that the infection must be treated and cleared by a doctor before she can enroll in the study. Usually, UTIs are treated successfully with a week-long course of antibiotics. Ask how the infection is being treated. If the candidate has no doctor you can recommend one from the list.

8.7.16 Questions 16 and 16a

If the candidate is not in an intensive weight loss program, mark the bubble "No", do not answer 16a, but proceed to question 17. **Long-term weight loss maintenance programs, such as Weight Watchers, Take Off Pounds Sensibly (TOPS), or Overeaters Anonymous (OA) are not considered "active" weight loss programs and do not exclude the candidate.** If the candidate is in one of these or similar long term weight loss maintenance programs you should mark "No" to this question and proceed to question 17.

If the candidate is enrolled in an intensive weight loss program mark the "Yes" bubble and go to question 16a. If the candidate is enrolled in a short-term, active or intensive weight loss program, it will be impossible to evaluate the effects of PRIDE's weight loss intervention. Therefore, candidates must be willing to stop any current intensive weight loss program in order to qualify for PRIDE.

It is important to ascertain whether the candidate is in a weight loss program that is prescribed and monitored by a health care provider. In this case, even if she is willing to stop, she must obtain a letter of agreement from that health care provider that she can stop her current program for approximately 22 months. In such cases, continue screening but note on the Participant Tracking Log that a "clearance to participate" letter must be obtained prior to Randomization. Tell the candidate you will mail her some information and a form for her health care provider to sign and fax to the PRIDE site.

If the candidate is enrolled in a self-initiated active weight loss program and is willing to stop, she can continue screening. However, a note should be made on the log sheet to confirm during the Screening Visits that the weight loss program has been discontinued.

As mentioned earlier, the investigator may choose to avoid screening women who have participated in intensive weight loss programs at her/his clinical site within the past 5 years since the intervention materials will be too similar. Please document the number of candidates who are not suitable study candidates due to previous participation in local intensive weight loss programs and provide these numbers to the Coordinating Center at the end of enrollment.

8.7.17 Question 17

This question refers to **prescription medications** only. If the candidate is not taking any prescription medications for urinary incontinence or for weight loss then mark the bubble "No" and go to question 18.

If the response is "Yes", go to question 17a.

8.7.18 Question 17a

Ask the candidate to tell you the name of any prescription medication she is taking and compare that with the list of exclusionary medications in 17a and in Additional Medication List, Appendix 8C. (The Additional Medication list has been designed to capture new medications that have been approved since PRIDE started.) **Fill in the bubble "Yes" or "No" for each medication.** If the medication(s) is listed in Appendix 8C, please mark "yes" for item 17aV and indicate the code number of the medication(s) in the field(s) provided. If the medications marked with an asterisk are prescribed for depression rather than incontinence, then fill in the bubble "No" beside that medication. If the participant can't remember the names of her medications and doesn't have them handy read the list to her to her and mark "Yes" or "No" for each medication on the list. Proceed to question 17b. Please note that if you fail to mark "Yes" or "No" for each medication a query will be generated.

If all the medications are marked "No", ask the candidate to read the name of her prescription medication if possible and , double check the lists. If the medication is not on either list, make a correction to the form by crossing out the "Yes" response to question 17, marking the "No" response and circling it, and drawing a diagonal line across the list of medications. Initial and date the correction. Go on to question 18.

Please note – If a participant is taking a new exclusionary medication for incontinence, weight loss, diabetes, or a new steroid, please notify the Coordinating Center and request that the Additional Medications List be updated accordingly.

8.7.19 Question 17b

If the candidate is willing to stop her prescription medication she must first call the prescribing physician, obtain a letter of agreement and discontinue the

medication under the physician's guidance. If the candidate is willing to do this, offer to mail her information and a form for the physician to sign and fax to the PRIDE site. Make a note on the Participant Tracking Log that the medication must be discontinued and a letter received from the health care provider by the time of the randomization visit.

If the candidate is not willing to stop the prescription medication that she is taking for weight loss or incontinence she is not eligible for PRIDE. Fill in the bubble "No" and skip to question 30.

8.7.20 Questions 18 and 18a

The PRIDE staff cannot provide primary medical care for the candidate. If the candidate does not have a primary health care provider (fill in the bubble "No" to question 18) but is willing to find one (fill in the bubble "Yes" for question 18a) you may continue screening. Make a note on the tracking log that this issue should be resolved prior to the Randomization Visit. You may help by providing names from a list of local Primary Care Physicians who are willing to take referrals. If the candidate does not want to initiate contact with a physician, she is not eligible for PRIDE. In this case, fill in the bubble "No" for question 18a and skip to question 30.

8.7.21 Question 19a - d

Read question 19 to the candidate and then read each of the medical conditions/procedures in questions 19a, 19b, 19c and 19d. Fill in the bubble "yes" or "no" for each item. If any of the responses is "yes", the candidate is not eligible for the study and you should skip to question 30.

19a and 19b. Cancer of the pelvis, including uterine, ovarian, vaginal or cervical cancer exclude the candidate from the study even if this condition has been treated successfully with radiation or with medical therapy. Women who have had cervical or vaginal dysplasia (non-invasive cervical neoplasm) are eligible to continue screening.

19c. Urethral surgery is surgery on the urethra, the tube that carries urine from the bladder to the outside. This may be done to relieve an obstruction, repair a defect (urethral diverticulum) or to treat incontinence. Women who have had urethral dilation which was NOT done specifically for the purpose of treating or improving urinary incontinence are eligible to continue screening.

19d. The following surgeries for urinary incontinence exclude the candidate: needle urethropexy (Peyera, Stamey, or Raz), retropubic procedures (Burch, Marshall-Marchetti-Krantz, or Tanago colposupension procedure), sling procedures, tension-free vaginal tape (TVT), intra-vesical therapy (botox), and/or urethral bulk injections (Durasphere, collagen). Women who have had anterior repair or cystocele repair which was NOT done specifically for the purpose of treating or improving urinary incontinence are eligible to continue screening. If there are questions about whether specific types of surgery exclude a participant, call the Coordinating Center for advice.

"Bladder raised" is a common description for a procedure done for incontinence; it is also a layman's term for an anterior vaginal repair that was once thought to improve incontinence but now is proven not to be effective. If a candidate reports having had her "bladder raised" she is NOT eligible for PRIDE, unless she can provide additional information on the surgery. If she had a vaginal hysterectomy and repair of her vagina (anterior repair, anterior colporrhaphy) without a sling or other suspension, she is eligible. (It is very common for a woman to have a vaginal hysterectomy with repair of the vagina – her gynecologist will tell her the surgery will lift her bladder, which is true, but this is not an effective surgery for incontinence).

8.7.22 Question 20a - d

Read question 20 to the candidate and then read each of the medical conditions/procedures in questions 20a, 20b, 20c and 20d. Fill in the bubble "yes" or "no" for each item. If the candidate reports "chest pain" or "difficulty breathing" ask if she has seen a doctor for her symptoms. Probe to determine the correct diagnosis. If this is unclear, consult the Principal Investigator or Coordinating Center for direction. If any of the responses are marked "yes", continue to question 20e.

8.7.23 Question 20e

Candidates with coronary heart disease must have permission from a cardiologist or primary care physician to participate in PRIDE. Even though the exercise program is not considered strenuous, the candidate may have been sedentary for a long time and caution is prudent. Ask the candidate if she is willing to obtain written approval from a medical professional to participate in the study. If she says "yes", she is eligible to continue screening. You can offer to send study information and a form for her doctor to sign and fax to the

PRIDE site. Make a note on the tracking log that a letter is expected prior to Randomization. Candidates currently enrolled in Cardiac Rehabilitation programs must finish these before being screened for PRIDE. Continue to question 21.

8.7.24 Question 21

If the candidate is a diabetic fill in the bubble "yes" for question 21 and proceed to answer question 21 a, and, if applicable, question 21 b and/or 21c. If the candidate is not a diabetic or doesn't know, fill in the appropriate bubble and skip to question 22.
Please note: if the response to question 21a is "Don't Know" be sure to flag the candidate for further follow-up. Insulin-dependent diabetics and diabetics on some oral medications are not eligible for the study. The method of treating their diabetes must be clarified before randomization can occur.

8.7.25 Questions 21a - c

Women who consider themselves to be diabetic but have been told they don't need treatment or don't know if they are treated for diabetes are eligible to continue screening. Fill in the bubble "No treatment" or "Don't Know" and skip to question 22.

For question 21a, you must indicate all the responses that apply to the candidate. For instance, she may be on a calorie-restricted diet as well as taking oral medication for her diabetes. If so, fill in both these bubbles.

If the candidate is taking oral medication, fill in the appropriate bubble, then ask question 21b and read the list of medications. Fill in the bubble "Yes" or "No" for each of the drugs listed. If "Yes" is marked for any of the categories listed, the candidate is not eligible and you should skip to question 30. If the response is "No" to all of the medications listed, ask the candidate to tell you which medication she is taking. Make sure this is not a variation of one listed. Other oral anti-diabetic agents are allowed. Proceed with screening.
If the candidate is insulin-dependent, please fill in the appropriate bubble and ask question 21c. All current insulin products are listed on the Eligibility Form, thus the response to this question should be "Yes". Fill in the bubble "Yes" and skip to question 30. If the candidate answers "No" or "Don't Know" she may be confused, and this issue must be resolved when she brings all her

medications to a clinic visit. Mark the appropriate bubble and continue to question 22.

8.7.26 Question 22

Candidates who have not had cancer or don't know if they have had cancer **in the past 5 years** are eligible to continue screening. Mark the appropriate bubble and skip to question 23.

If the candidate has had cancer (except non-melanoma skin cancer) **in the past 5 years** fill in the "Yes" bubble and answer questions 22a – 22c.

NOTE: candidates with prior urogenital cancer (uterine, ovarian, vaginal or cervical cancer) at any time in the past would be excluded from study participation in question 19.

8.7.27 Questions 22a - c

Cancers that exclude the candidate, regardless of when the cancer occurred, are: uterine, ovarian, vaginal or cervical cancer. Women who have had cervical or vaginal dysplasia or Squamous Intraepithelial Lesion (SIL) (non-invasive cervical neoplasm), are eligible to continue screening.

For cancers that are not in the urogenital tract, the candidate must be cancer-free for at least 5 years.

8.7.28 Question 23

Medical conditions such as AIDS or HIV compromise the immune system and may directly or indirectly lead to problems or medications that confound the study results. Therefore, if the response to this question is "Yes", the candidate is not eligible and you should skip to question 30. If you are concerned that the candidate may find this particular question discriminatory, you may continue with the remainder of the screening questions and be non-specific about the reason for lack of eligibility.

8.7.29 Questions 24 and 25

If a candidate is unable to walk 2 blocks without stopping or needs a cane or walker, she is unlikely to be able to engage in the prescribed exercise program

and is not eligible for the study.

8.7.30 Question 26

A candidate is not eligible for the study if she is planning to move to a location that makes it impossible to attend study lessons or visits. A move that is closer to the PRIDE site or has no impact on study participation should be marked as a "No" response.

8.7.31 Question 27

While planned travel is not an exclusionary criterion, it may impact the candidate's ability to attend the intervention sessions or the study visits. Make a brief note in the boxes provided on the form (for example, "FREQUENT TRAVELER") and notify the Study Coordinator or Principal Investigator prior to the Orientation Visit.

8.7.32 Questions 28 and 28a - b

If the candidate is not enrolled in any other type of research project fill in the "No" bubble and continue to question 29. If the response is "Yes", fill in the "Yes" bubble and answer questions 28a and 28b. Most research studies involving active interventions prohibit candidates from enrolling concurrently in another trial. If the candidate is taking a study-prescribed medication or following a study-prescribed behavioral change program such as diet or exercise, she is not eligible for PRIDE. If she is enrolled in a long-term non-interventional study (for example, an observational trial such as the Nurses' Health Study), she is eligible for PRIDE. Please confirm eligibility by discussing this situation with the Principal Investigator.

8.7.33 Question 29

Ask how the candidate heard about PRIDE and mark all responses that apply.

8.7.34 Question 30

Choose the ONE response that best suits the candidate's eligibility status at this time.

- If the candidate is eligible and willing, mark the "**Eligible**" bubble

and make an appointment for the candidate to attend the first available Orientation session.

- If you have skipped to question 30 because the candidate is not eligible for PRIDE please mark the "**Not Eligible**" bubble and enter the number of the question on the Eligibility form that led you to conclude the candidate should be excluded. If this is a sub-category to a question you must enter the sub-category letter also (for example 22c or 28b). Please see section 8.8 for instructions about re-screening candidates.
- If the candidate appeared to be eligible but was unsure about her commitment, has to wait for a day or a nighttime cohort, had to check with a doctor and was unsure about her/his approval, etc. then fill in the bubble "**Pending**" and schedule a time to call her back for resolution. The eligibility form should be faxed to the Coordinating Center at this time. When the issue that is pending is resolved, the Study Coordinator should post a query on the Website and make a correction to question 30, changing the Eligibility Status to the appropriate final status of the candidate. If you select "pending" please be consistent with the way you express the reasons. For example, please enter "Day Group" or "Night Group" as appropriate, if the candidate is to be held for the next session. Reminder: If the interval between the Eligibility Screening and the Orientation session is more than 3 months, then all questions on the Eligibility Screening form must be reviewed with the participant before proceeding with Orientation. Post queries as necessary to correct information that has changed.
- If the candidate is eligible but is **unwilling to participate**, mark the last bubble, thank her very much for her time and encourage her to call back if she should change her mind.

8.8 RE-SCREENING

You may re-screen a candidate at a later time if she fails to meet entry criteria that may or will change (for example, age, pregnancy status, participating in an intervention trial that is ending soon, insufficient incontinence episodes etc.). When a candidate is re-screened she must be assigned a new, unique ID number and an entire new set of data forms must be completed. The new ID number should be recorded on the Participant Tracking log along with the original ID number. At the end of the recruitment period the study coordinator should provide a list to the Coordinating Center of all candidates who have been re-screened, identifying all ID numbers used

for the same person.

8.8.1 Re-Screening Due to Change in BMI Entry Criterion

In July, 2005 the PRIDE DSMB approved a proposal from the PRIDE Steering Committee to expand the Body Mass Index entry range from 25 – 45 kg/m^2 to 25 – 50 kg/m^2. Several women who did not meet entry criteria during the initial telephone interview or when they were first weighed at the clinic may be re-screened now.

In ALL cases where you are re-screening due to expanded BMI criteria, please assign a new ID number and start all over as though this were a new participant. Be sure to indicate in the participant tracking log that this participant is a re-screen. Assign a new number, print new, updated data forms and complete all forms and procedures as you would for any new candidate, regardless of the length of time that has elapsed since the woman was first screened.

Please remember that you should not be conducting any screening according to the new criteria until Protocol Amendment #3 has been approved by your IRB.

8.9 SCREENING SCENARIOS

Once an eligibility form has been sent to the Coordinating Center for an eligible candidate, the status of that candidate must be tracked and documented. Appendix 8B is a summary of various situations that may occur during screening with an indication of the forms to be used to document each.

APPENDIX 8A

PRIDE TELEPHONE SAMPLE SCREENING INTERVIEW SCRIPT

Interviewer note: if you are the individual placing or returning a call and are not able to speak to the potential participant, just say that you will call at another time. Do not give details of the study to another person in the household. Respect the confidentiality of the respondent – she may not want anyone to know she is thinking about participating in a study about incontinence or weight loss.

Hello, my name is _____.

May I please speak to _____?]

I'm calling from the _____[say name of institution]_____ in response to your interest in the PRIDE study.

Do you have a few minutes to talk now?

__ Yes __ No - When may I call back?

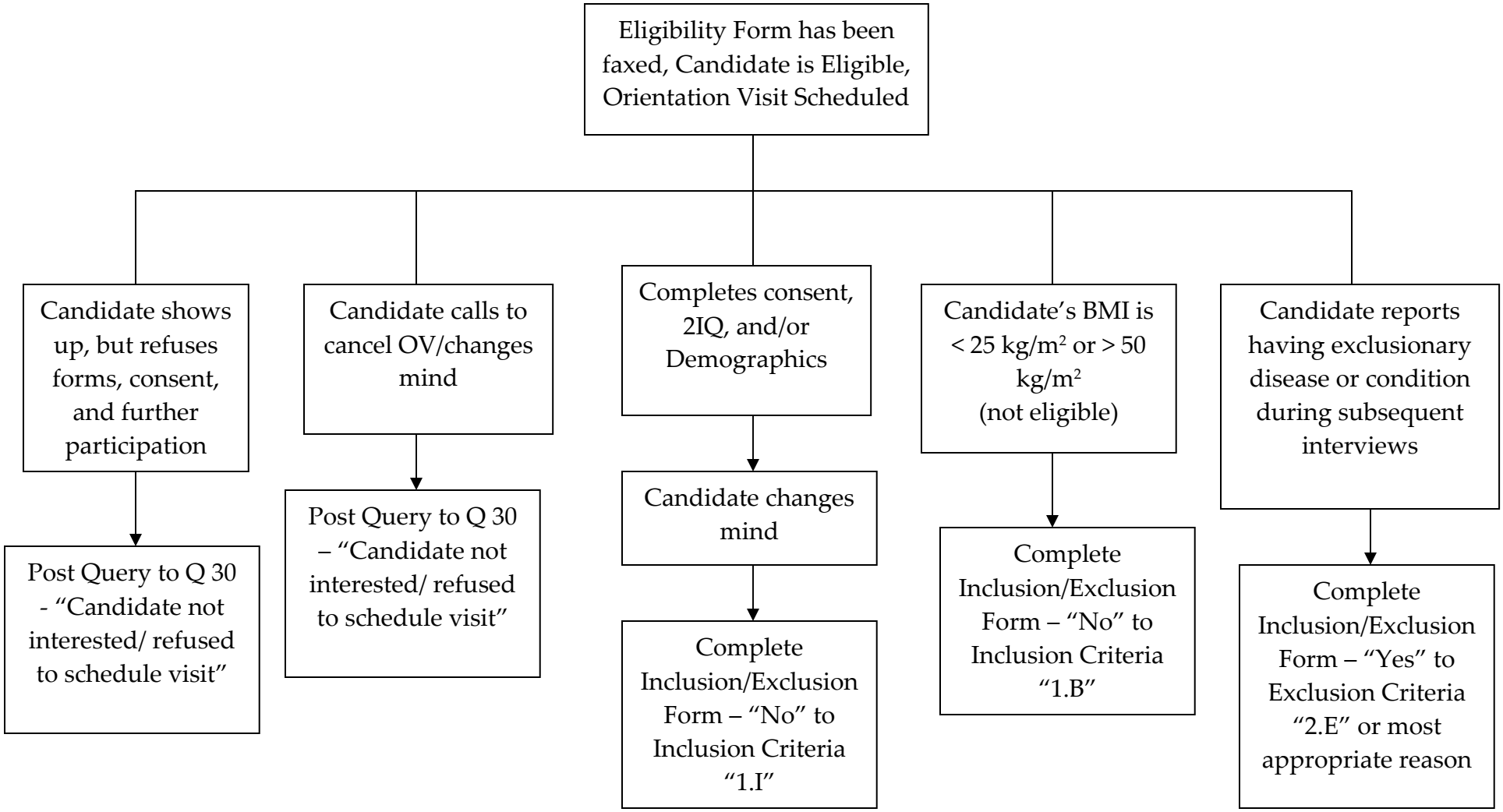
First, I would like to tell you a little about the study. Urinary incontinence or involuntary leaking of urine is a condition that affects thousands of women, in particular women who are overweight. This is a study to determine whether losing weight can help relieve the symptoms of urinary incontinence. The study lasts 18 months. It involves several group classes led by behavioral experts to promote weight loss by diet and exercise; and we provide information about exercises that can help control incontinence. There will be questionnaires that you can fill out at home and measurements taken at our clinic to see if there are changes in weight and changes in the number of times you leak urine. Are you interested in answering some questions to see if you would be an eligible candidate for the study?

___ Yes – proceed with interview

___ No

Thank you for your time. If you should change your mind, please feel free to call us at ( ) _ _ _ - _ _ _ _ .

Appendix 8B



NOTE: During screening, on the Inclusion/Exclusion form, mark **only one** most important reason why candidate is not eligible. **Leave all other reasons blank**.

APPENDIX 8C
ADDITIONAL EXCLUSIONARY MEDICATIONS LIST

Use of the following medications at baseline excludes the participant from participating in PRIDE:

No.	Brand	Generic	Classification
01.	Enablex	darifenacin	Incontinence
02.	Levsinex Timecaps	hycoscymine	Incontinence
03.	Sanctura	trospium	Incontinence
04.	VESIcare	solifenacin	Incontinence
05.	Decadron	dexamethasone	Steroids
06.	Cortone	cortisone	Steroids
07.	Orapred, Pediapred, Prelone	prednisolone	Steroids
08.	Sterapred, Sterapred DS		Steroids
09.	Tenuate, Tenuate dospan	diethylpropion	Weight Loss
10.	Adipex-P	phentermine	Weight Loss

CHAPTER 9

ORIENTATION VISIT

9.0 ORIENTATION VISIT

9.1 OVERVIEW

Orientation Visits (OV) are group visits to which eligible respondents are invited after the Eligibility Screening interview. This visit can be useful to:

- efficiently explain the study purpose and requirements and create enthusiasm for the study
- provide an opportunity for attendees to experience motivational aspects of the "group" encounter
- assess the likelihood of participant adherence to a lesson or visit schedule

9.2 OV VISIT SCHEDULE

The site will schedule, in advance, a series of Orientation Visits so that an interviewer will be able to offer dates, times and locations to candidates who are eligible and willing after the Eligibility Screening interview. Optimally, some evening or weekend sessions should be available. A confirmation letter and directions will be mailed to the candidate at least one week in advance of the OV. Include in the letter a reminder to bring glasses if needed for reading or for viewing the slide presentation.

9.3 ORIENTATION PROCEDURES

Forms/Logs Needed for this Visit:

- Screening Visit Checklist
- Brief or Full Informed Consent/HIPPA Authorization
- 7-day Voiding Diary #1
- 2IQ (on-site or take-home)
- Demographics (on-site or take-home)
- Contact Information (local form)
- Physician Consent Forms (local form)
- Participant Tracking Log

The investigator or designated staff will explain the purpose of the study (using the slideshow if you wish) and will describe the intervention, the random group assignments, the study schedule and the informed consent document. It may be helpful to let participants know that, if they qualify and participate, they will receive attention

from experts in weight loss and incontinence. Questions should be invited from the audience, and general eligibility and interest level assessed.
Informed consent will be obtained at this time. At the discretion of the investigator, consent can be either a brief consent to fill out a 7-day voiding diary or the main study Informed Consent.

At the end of the Orientation, the participant will be asked to fill out the 2IQ form (see Chapter 9.3.2), or to complete it at home and bring it back to SV1. The Study Coordinator or designated staff person will meet individually with each attendee to explain in detail the 7-day Voiding Diary which the participant will complete at home prior to SV1 (please see Chapter 9.3.3).

9.3.1 Informed Consent and Health Information Portability and Accountability Act (HIPAA) Compliance

9.3.1.1 Informed Consent

Informed consent must be obtained from each candidate before any data is collected.

Purpose: Extensive efforts should be made to inform candidates fully of all aspects and obligations of the study, the risks and benefits and the randomization odds.

Procedure: After the candidate has had the opportunity to discuss the study with clinic personnel and have any questions answered, she will be asked if she wishes to participate in PRIDE. She will be asked to read, fill out, sign and date the PRIDE Informed Consent Form in accordance with Federal Regulations and the guidelines set by local Institutional Review Boards (IRBs). Inform the participant that we are required by federal law to obtain fully informed consent for each aspect of the trial. Encourage the participant to ask questions if she does not understand any aspect of the form. It is very important that the participant is fully informed and enters the study freely and with a clear understanding of all study requirements.

Informed Consent Forms must be approved by local IRB prior to the start of the study. The original signed form should be filed in the participant's study binder and a copy should be given to the participant.

A copy of each clinic's approved Informed Consent Form and local IRB

approval will be kept on file at the Coordinating Center.

9.3.1.2 HIPAA

Purpose: The Health Information Portability and Accountability Act (HIPAA) requires that research participants give authorization for use of protected health information (PHI), defined as identifiable private information from medical records.

Procedure: Please follow the HIPAA procedures as defined at your institution. The original signed HIPPA form should be filed in the participant's study binder.

9.3.2 The Two Incontinence Questionnaire (2IQ)

This is a one page, 2-item, self-administered questionnaire designed to diagnose the type of urinary incontinence experienced by the participant. The accuracy of this brief questionnaire is being tested versus extensive medical assessments in a concurrent urinary incontinence trial. This questionnaire should be completed early in the study before the participant receives any training or information about incontinence.

The introductory, unnumbered question checks that the participant has leaked some urine in the last 3 months. If the response is "No" the participant is not eligible for the study and the coordinator should review the Eligibility Screening form to check for erroneous information about current incontinence.

Questions #1 and #2 can have multiple responses. Participants are asked to fill in all bubbles that apply. When this is completed the form should be reviewed at the clinic and faxed to the Coordinating Center data system.

9.3.3 7-Day Voiding Diary

The 7-day Voiding Diary will be collected once during Screening to determine eligibility, then again at the Randomization Visit, and at Months 6, 12 and 18. This diary is a primary outcome measurement for PRIDE and it is extremely important that the participant understands how to fill out the diary.

Two versions of the voiding diary are available – a short and a long version. The long version should be given to all participants initially. It allows for the

recording of up to 40 episodes of urinary incontinence daily and has one extra page at the back. The shorter version allows for the recording of up to 18 episodes daily and has two extra pages at the back. The short version may be used when the initial diary has been reviewed and it seems unlikely that the participant will need space provided by the long version.

Every effort should be made by study staff to encourage participants to fully complete all diary information and bring the diary to the next visit. Suggest that the participant carry the diary with her every day for seven days. If she is unable to do this suggest that she record her episodes on a piece of paper and transcribe them at the end of the day.

Staff will hand write Subject ID # and acrostic on ***every*** diary day page. Use the instructions on the inside cover of the diary to explain, in detail, diary entry procedures to the participant. For 7 days, she should record every time she urinates in the toilet and leaks urine.

Using a calendar, mark the scheduled date of the participant's Screening Visit 1 and arrange a mutually agreeable start date for the diary, keeping in mind that she must start it at least 8 days prior to the next study visit. We recommend that the participant start the diary ***the morning after*** she receives it. If this is not feasible discuss with the participant an alternate day to start the diary. Ideally she will fill the diary out daily for 7 consecutive days and bring it back to the next visit. If she forgets a day, instruct her to continue recording beginning the day after the one she forgot and to finish 7 complete days.

Written instructions for how to fill out the diary are included at the beginning of the diary and in Appendix 9A. Appendix 9A includes a sample reminder letter for participants also. Ask the participant to strike through "Page 2" any time she does not need these extra spaces. This will make it easier for you and she to review the diary later.

Review the symptoms of "Urge" vs "Stress" incontinence with the participant. Tell her to mark "Other" only if her leaking episode doesn't seem to fit either Urge or Stress. Ask her to describe very briefly in column 4, what she was doing when she leaked urine, especially if she marks "Other". She does <u>not</u> have to write in column 4 if she urinates in the toilet <u>without</u> leaking. Explain that you will review her diary with her when she returns. Tell the participant that she can call the Study Coordinator to ask questions while completing the voiding diary. When you are finished explaining the diary:

- determine if the participant has any questions about how to complete the diary
- provide a couple of hypothetical scenarios and ask her to tell you how she would record these in the diary
- remind the participant to bring the completed diary with her to the next visit
- if she can't start the diary the next morning, make a note of when she plans to start and call her the day before to remind her that she is to start the diary the next day

Occasionally, it can be a challenge for the participant to identify the type of incontinence episode she has experienced. Here are some examples that may be helpful:

1. Leaking upon standing up – this may be a urine flow that hasn't quite finished (not an incontinent episode), pressure on the bladder when standing (stress incontinence), or a sudden need to urinate again (urge incontinence). It is important to have the participant describe the episode in as much detail as possible to help her determine the nature of the leaking.
2. Leaking when sleeping - this may occur when obese participants roll over and put pressure on the bladder (stress) or because they have dreamt they are on the toilet (urge). Probe for as much information as possible. If most other episodes marked on the diary are urge episodes it is likely that bed-wetting is also. Note that a report of "waking up wet" is an episode that should be recorded on the diary for the previous night.
3. Leaking on the way to the bathroom is usually urge incontinence. Hearing or feeling water often creates urge.
4. Leaking described as "just had to go" is usually urge incontinence.

9.4 SCHEDULING SV1

At the end of the OV, a Screening Visit 1 should be scheduled to take place at least 8 days after the Orientation Visit (to allow time to complete the 7-day Voiding Diary) but no longer than 9 months from the Eligibility Screening (ES) date (see Ch.9.4.1).

The participant should leave the Orientation with the following packet of forms to fill out at home:

- Contact Information/Physician Forms (local)
- Demographics Form (if not completed in clinic)
- 2IQ (if not completed in clinic)
- 7-day Voiding Diary

9.4.1 SV1 DELAYED FOR NEXT COHORT

If the SV1 is scheduled more than three months after Eligibility Screening to facilitate the formation of intervention groups, then the Eligibility Screening Form must be reviewed and eligibility information must be updated as necessary before the SV1 takes place. **The participant keeps the same ID number.** The participant may be invited back for a refresher Orientation.

If a participant attends an Orientation Visit, completes the 2IQ and Demographics form, and then is held for the next cohort:

1. Post a query to Q30 on the Eligibility Screening Form
   - Select "Pending" and indicate "Day Group" or "Night Group"
2. Indicate on the Participant Tracking Log that the candidate is waiting for the next cohort.

When screening begins for the next cohort, eligibility items (weight, weight loss, exclusionary medications, etc) should be reviewed with the candidate, if three or more months have passed. If information has changed slightly but <u>does not change</u> eligibility status, you do not have to make any changes to the ES form. If the candidate is still eligible, she can attend an Orientation Visit again or schedule Screening Visit 1. The candidate does <u>not</u> have to complete the 2IQ or Demographics form again.
If the candidate is no longer eligible when the Eligibility Screening form is reviewed, post queries and edit the information that has changed. Post a query again to Q30, select "Ineligible" and enter the number of the question that now makes the candidate not eligible for PRIDE.
For more details, please review the "Guidelines for Delayed Screening Schedules in PRIDE" attached as Appendix 9B.

Appendix 9A

INSTRUCTIONS

COMPLETING THE 7-DAY VOIDING DIARY AT HOME

Dear PRIDE Participant:

Enclosed is a 7-day Voiding Diary for the PRIDE study.

Here is what we are asking you to do:

1. Please carefully read the instructions on how to complete the diary.

2. Please start this diary the morning **after** you receive it.

3. If you have ANY questions, please call the study coordinator at the PRIDE Study Clinic: _____

4. Bring your completed diary to your next visit at the PRIDE Clinic.

   Your next Appointment: _____ at_____
   (date) *(time)*

5. If you have not completed your diary before your scheduled visit, call the study coordinator at the PRIDE Study Clinic to reschedule the visit.

How to Complete this Diary

When to start the diary:

- Begin recording information **when you get up for the day**.
- If you wake up during the night or early morning (before you get up for the next day), continue recording on the diary day that you have already started.
- Begin a new diary day each morning when you get up for the day.

How to complete the diary:

A. Record the day of the week and the date you started the diary.
B. Record the time when you got up for the day.
C. At bedtime, record the time you went to bed for the night.
D. After completing the diary day, indicate whether you recorded each time you urinated or leaked.

How to record when you urinate or leak:

1. "TIME" **Write the time each urination occurred. Be sure to check (√) the AM or PM box.**

2. **"DID YOU URINATE IN THE TOILET?"** Check (√) yes if you urinated in the toilet at all. This may or may not include leakage.

3. **"DID YOU LEAK URINE?"** Check (√) yes if you leaked urine of any amount. Leakage could range from a few drops to a large accident.

- NOTE: There may be instances when you need to check (√) Yes for #2 **AND** #3 on the same entry.

3a. **"REASON FOR LEAKAGE"** If you check (√) yes on the column, "DID YOU LEAK URINE?" you should **always** indicate the **main** reason for the leakage by checking only **one** of the three boxes in the next column labeled, **"REASON FOR LEAKAGE."**

"Urge" Check (√) this box if you leaked because you felt an urge or pressure to urinate and felt that you couldn't make it to the bathroom on time.

" Stress" Check (√) this box if you leaked because of coughing, sneezing, laughing, lifting something heavy, moving too quickly, or other physical activity.

"Other" Check (√) this box if you had urine leakage that was not an "Urge" or "Stress" leakage.

4. **"WHAT WERE YOU DOING?"** Please write down what you were doing at the time of this episode, for example, running, coughing, or cooking.

If you run out of room on your diary:

- Each diary day has two pages. If you run out of room on Day One, page 1, go to Day One page 2. If you run out of room on Day One, page 2, use the "EXTRA ENTRIES" page at the back of the diary.
- When using the "EXTRA ENTRIES" page, please write the date when each urination occurred. Note that this "EXTRA ENTRIES" page can be used for all seven diary days.

IF YOU HAVE ANY QUESTIONS PLEASE CALL _____

Appendix 9B

Guidelines for Delayed Screening Schedules in PRIDE

As of October 28, 2004, the maximum allowed interval between the Eligibility Screening interview and the randomization visit has been extended to 9 months. There will be no restrictions on the intervals between the Eligibility Screening, OV, SV1, SV2 and RV. These changes facilitate the accumulation of groups for intervention sessions. The extension of screening time does not change the entry criteria for the study. Eligibility criteria should be reviewed periodically as follows:

A. If the interval between Eligibility Screening(ES) and Orientation Visit (no other forms completed) is more than 3 months, all questions on the Eligibility Screening Form (ESF) must be reviewed with the candidate before proceeding with further visits The interviewer should post queries for the ESF and update Q.30 as necessary.

B. If the candidate has completed one or more screening visit forms (apart from the ESF) AND the duration between Screening Visit 1 and Randomization Visit is more than 3 months, the following items must be rechecked:

Check if done:	**Recheck:**	**Form:**	**Action:**
☐	Body Mass Index (BMI)	Review *Eligibility Screening Form* (ESF) Question 10 with the candidate.	If *Height and Weight form* was already completed AND the candidate's BMI is now out of range, she is still eligible. Continue with screening. If *Height and Weight form* was <u>not</u> completed AND the candidate's BMI is now out of range, she is not eligible. Complete the *Inclusion/Exclusion Form* and mark "No" for criteria 1B.
☐	Weight loss of 10 pounds or more	Review *ESF* Question 11 with the candidate.	If candidate has lost 10 pounds or more in the last 3 months, she is not eligible. Complete the *Inclusion/Exclusion Form* and mark "Yes" for exclusion criteria 2B.
☐	Weight loss	Review *ESF*	If candidate has started a weight loss

	program	Question 16 with the candidate.	program AND is willing to stop, no action is needed. If candidate has started a weight loss program AND is <u>not</u> willing to stop, complete the *Inclusion/Exclusion Form* and mark "Yes" for exclusion criteria 2B.
☐	Medications	Review *ESF* Question 17 with the candidate to check for new medications.	If candidate has started a weight loss or incontinence medication AND is willing to stop, no action is needed. If candidate has started a weight loss or incontinence medication AND is <u>not</u> willing to stop, complete the *Inclusion/Exclusion Form* and mark "Yes" for exclusion criteria 2A. If the *Medications Form* was completed and the candidate has new medications, the *Medications Form* should be updated by posting a query.
☐	New diagnosis or medical condition	Review *ESF* Questions 8, 15, 19, 21-26 and *Health History Form* Questions 16a-16g with the candidate.	If the candidate is not eligible, do not post queries to the *ESF* or *Health History Form*. Complete the *Inclusion/Exclusion Form* as follows: If candidate is not eligible because of: ESF Q.8 ◎ mark "Yes" for exclusion criteria 2C. ESF Q.15 ◎ refer candidate for treatment. She is eligible to continue screening after treatment. ESF Q. 19 ◎ mark "Yes" for exclusion criteria 2F. ESF Q. 21 ◎ mark "Yes" for exclusion criteria 2H. ESF Q. 22 ◎ mark "Yes" for exclusion criteria 2H.

			ESF Q. 23 ◎ mark "Yes" for exclusion criteria 2H. ESF Q. 24 ◎ mark "No" for inclusion criteria 1J. ESF Q. 25 ◎ mark "No" for inclusion criteria 1J. ESF Q. 26 ◎ mark "Yes" for exclusion criteria 2I. HHx Q.16a-16g◎ mark "Yes" for exclusion criteria 2E.
☐	Participation in a research study	Review *ESF* Question 28 with the candidate.	If the candidate is not eligible, complete the *Inclusion/Exclusion Form* and mark "Yes" for exclusion criteria 2J.

CHAPTER 10

SCREENING VISITS

10.0 SCREENING VISITS

10.1 OVERVIEW

Two Screening Visits will be completed prior to the Randomization Visit. The visits have been designed to provide as much flexibility as possible for investigators and participants. Most questionnaires are self-administered forms than can be completed at home or in clinic, and most forms or procedures can be done at either of the two screening visits. There are no specified intervals between these visits.

10.2 PURPOSE OF THE SCREENING VISITS

The Screening Visits are used to establish eligibility for the study and to collect baseline information that will be used to test the trial's hypotheses.

10.3 SCREENING VISIT 1 (SV1)

10.3.1 Preparation for SV1

SV1 is the participant's first individual clinic visit. Call to remind her about the appointment time, length of time it will take and to bring with her the take-home forms and diary she was given at the Orientation Visit. Print out the SV1 data forms from the PRIDE website. (Any form or questionnaire with "SV" as a visit box choice can be done at either SV1 or SV2.) **The forms followed by an asterisk in the box below are used to collect information that is critical for participant eligibility.**

Forms/Logs needed during Screening Visit 1:

- Screening Visit Checklist (to be updated)
- Informed Consent/HIPPA (if not signed at OV)
- 7-day Voiding Diary #1 (if not presented at OV)
- 7-day Voiding Diary Data Entry Form* (SV)
- Vital Signs*
- Height and Weight*
- Health History Form*
- Dipstick Urine Analysis*
- 7-day Diet and Exercise Diary
- Paffenbarger Activity Questionnaire (take home)
- Food Frequency Questionnaire (take home)

- Incontinence Impact Questionnaire (take home)
- Urogenital Distress Inventory (take home)
- Health & Activity Form (SF-36) (take home)
- Inclusion/Exclusion Form* (to be updated)
- Participant Tracking Log (to be updated)

In addition to the forms and logs listed above, please have the following available:

- participant's binder with the participant's contact form, the completed Eligibility Screening form, Informed Consent form and HIPPA authorization
- an envelope or folder and PRIDE pen for the take-home questionnaires.

If the participant has not yet signed Informed Consent for PRIDE, she must do so before the SV1 begins (see Chapter 9.4).

10.3.2 SV1 Procedures

10.3.2.1 Review of the Take-Home Questionnaires

Collect and review the Demographics form and the 2IQ to be sure there are no missing values or mistakes. If mistakes were made and corrected, be sure to circle the correct response, initial and date the correction before the form is faxed to the data system.

10.3.2.2 Review of 7-Day Voiding Diary

Certified study staff will review the 7-day Voiding Diary for accuracy and completeness immediately upon receipt at the clinic. Enter the date of today's visit and your Staff ID# on every completed diary page as you review it with the participant. Be sure the participant's ID number/acrostic is entered on every completed page.

If the participant has not filled out the diary correctly or completely for at least 5 of the 7 days, or if she has not had at least 10 episodes of incontinence, **the participant is not eligible** for PRIDE. In this case, you should cancel the remainder of the visit. You may either allow the participant a second chance by giving her another diary and another

SV1 appointment OR complete the Inclusion/Exclusion Checklist marking "no" for Inclusion Criteria, item I.

Ideally, the diary should reflect 7 consecutive days of the participant's experience. However, **gaps in recording days** are admissible up to a limit of two weeks. If the participant forgets to record for a day, or fails to record days due to extenuating circumstances (e.g. a family emergency), she should continue the diary as soon as possible, entering the correct day and date at the start of the page. If the gap in recording is 14 days or more the diary is inadmissible. If the participant had a legitimate and unique problem that led to the interruption she should be instructed to start a new diary and the visit should be re-scheduled. If the participant simply forgot or was unreliable at documenting her experience, she is not eligible for PRIDE. In this case, complete the Inclusion/Exclusion data form, marking "no" for Inclusion Criteria, Item I.

The completed 7-day Voiding Diary should be kept with the participant's file at the clinical site. The Diary is not sent to the Coordinating Center unless requested.

Reviewer Instructions for reviewing the Diary:

1. Discuss the diary entries with the participant. If the diary is incomplete, probe the participant to complete as much missing data as possible.

   For ***each diary day***, the participant should have entered the:
   a. Day of the week and date
   b. Time she got up for the day (AM or PM)
   c. Time she went to bed for the night (AM or PM)
   d. Degree to which she recorded all episodes for the day
   e. Time each episode and whether AM or PM
   f. Urinations in toilet
   g. Leakages, and if she did leak, the reason for leakage
   h. What she was doing when she leaked

For each entry to be considered complete the participant must have a check in both column 2 (Did you urinate in the toilet? No or Yes) and column 3 (Did you leak urine? No or Yes) and each "Yes" check in

column 3 (Did you leak urine?) must be accompanied by one check in column 3a (Reason for Leakage). The participant should decide which of the three categories best describes her episode of urinary incontinence.

Examples of Mistakes on the Diary

A.

1. TIME	2. DID YOU URINATE IN THE TOILET?	3. DID YOU LEAK URINE?	IF YES ⇒	3a. REASON FOR LEAKAGE Please check only **one** main reason
7:30 ☑ AM ☐ PM	☐ No ☑ Yes	☐ No ☐ Yes	⇒	☐ Urge ☐ Stress ☐ Other

- Participant did not check No or Yes in column 3. Query the participant and have her check the appropriate response.

B.

1. TIME	2. DID YOU URINATE IN THE TOILET?	3. DID YOU LEAK URINE?	IF YES ⇒	3a. REASON FOR LEAKAGE Please check only **one** main reason
12:15 ☐ AM ☐ PM	☐ No ☐ Yes	☐ No ☑ Yes	⇒	☐ Urge ☑ Stress ☐ Other

- Participant did not check AM or PM in column 1. Query the participant (you can note the order of the entry in this day's diary) and have her check the correct response.
- Participant did not check No or Yes in column 2. Query the participant and have her check the appropriate response.

C.

1. TIME	2. DID YOU URINATE IN THE TOILET?	3. DID YOU LEAK URINE?	IF YES ⇒	3a. REASON FOR LEAKAGE Please check only **one** main reason
6:10 ☐ AM ☑ PM	☐ No ☑ Yes	☐ No ☑ Yes	⇒	☐ Urge ☐ Stress ☐ Other

- Participant checked Yes in column 3 (Did you leak urine?) but did not make a corresponding check in column 3a (Reason for Leakage).

Query the participant. Review time of entry and other responses to assist in recall of circumstances surrounding the event.

- **Reviewer:** "On day 3 at 6:10 PM you have recorded that you urinated in the toilet and you leaked, but you did not record the reason for leakage. Could you think back to this time? Try to recall what caused this leak and check the reason in column 3a."

2. Check to determine if the participant used the "Extra Entries" Page at the end of the diary. If the extra page was used, make sure that the participant entered the **date** of each episode in the left-most column.
3. Review the entries for what the participant was doing when she leaked. In particular, review what she was doing when she marked "Other" in column 3a, to confirm that these cannot be classified as "Urge" or "Stress" episodes. One example of "Other" might be "vaginal voiding". This occurs more often in very obese people with folds of thigh fat. Leakage may occur when the participant is sitting but is not noticed until she stands up.

Please review Chapter 8. 7. 13 for more typical scenarios of incontinence. If you are in doubt about how an episode of incontinence should be classified, please consult your site urogynecologist or call the Coordinating Center for guidance.

4. The reviewer should divide the diary into "**daytime**" and "**nighttime**" by drawing a line after the last void before the participant went to bed for the night. ("Nighttime" is based on the participant's bedtime). **Note:** If a diary entry was made at the same time as the participant's bedtime, the entry should be included in the "**daytime**" urinations category. In some cases participants have unusual schedules with no regular bedtime or wake-up times. In such a case, you do not have to draw a line; simply count all "sleeping" episodes as nighttime and all "awake" episodes as daytime.
5. Add up the number of 'checked' boxes in columns 2, 3 and 3a to obtain the total number of urinations in the toilet, the total number of leakages, the total number of "Urge" episodes, the total number of "Stress episodes and the total number of "Other" episodes. <u>This is a very important step – please recheck your additions when you have finished.</u> Enter the totals in the appropriate shaded boxes at the

bottom of each diary page. **The totals for the daytime and nighttime episodes should be added and recorded separately.** If the participant completes multiple pages on any day, add the totals on all pages together for that day. **For each column there is a "Daytime" and "Nighttime" total.** Do not add "No" responses to the total. The 5 columns include:

1.	Did you urinate in the toilet?	Total number of Daytime "Yes" responses only Total number of Nighttime "Yes" responses only
2.	Did you leak urine?	Total number of Daytime "Yes" responses only Total number of Nighttime "Yes" responses only
3.	Reason for leakage: Urge?	Total number of Daytime "Urge" responses Total number of Nighttime "Urge"responses
4.	Reason for leakage: Stress?	Total number of Daytime "Stress" responses Total number of Nighttime "Stress" responses
5.	Reason for Leakage: Other?	Total number of Daytime "Other" reponses Total number of Nighttime "Other" responses

10.3.2.3 Completing the VOIDING DIARY DATA ENTRY FORM

After reviewing the diary and totaling the episodes, fill in the VOIDING DIARY DATA ENTRY FORM. The Date of Visit is the day the participant returns with the completed diary. Enter the totals that you have calculated on the Voiding Diary. If the participant has filled in the diary completely and accurately, and if she has 10 or more episodes of incontinence recorded for a week, she is eligible to continue in the study. The diary will be considered complete and accurate if "All of the time", or "Most of the time" is marked on ***at least five diary days***. The reviewer should check to make sure that each episode marked has complete data.

- From the shaded boxes on the diary, enter the total daytime and nighttime episodes onto the data form. Check to make sure you included both pages for each day as well as any "Extra Entries" from the last page/s of the diary. Remember to add these entries into the totals for the date listed in the left-most column.
- Enter a zero in the corresponding boxes if the participant never answered **"yes"** to **"did you urinate in the toilet?"** and/or **"did you leak urine?"** on a given day.
- Fax the completed form to the data system at the Coordinating Center

10.3.3 Dipstick Urinalysis

Urinary tract infection may cause or worsen urinary incontinence. Therefore, participants who may have a urinary tract infection will be excluded. The dipstick urinalysis will be performed to detect possible urinary tract infection. A "clean catch" urine sample is required for the dipstick test.

Procedure:

- Give the participant a sanitary wipe and ask her to wipe the genital area to remove any bacteria prior to urinating
- Instruct the participant to start her urine flow into the toilet, stop the flow and then continue urinating into the urine container that has been provided. A participant instruction sheet is attached as Appendix 10A.
- About 1 ounce of urine is sufficient for the test
- Dip the reagent strip in the urine, remove, and compare each reagent area with the corresponding color chart on the bottle label at the elapsed time interval specified on the bottle.
- Participants with a normal result (negative) for leukocyte esterase and a normal (negative or trace) test for blood are eligible for the study.
- Complete the DIPSTICK URINALYSIS FORM.

Abnormal Results: The following abnormal results make the participant **ineligible** for PRIDE:

Leukocyte Esterase	Blood	Hemolyzed Blood
Trace	Moderate	Small (+)
Small (+)	Large	Moderate (++)
Moderate (++)		Large (+++)
Large (+++)		

Participants with any of the above results will be informed that they may have a urinary tract infection and/or blood in their urine and will be referred to a physician for follow-up. The screening procedures may continue as long as the participant is willing to have any problem treated, and to return for a repeat dipstick urinalysis. The dipstick test must be repeated even if blood is present due to menstruation.

10.3.3.1 Repeat Urine Dipstick

Treatment for a urine infection generally involves a week-long course of antibiotics. The test should be done at SV1 and repeated if necessary at SV2 after the participant has received effective treatment for a urinary tract infection. The dipstick urinalysis performed at a Urodynamic Study visit can serve as a repeat test if necessary**. The results of a repeat test should be recorded on a new data form with the appropriate visit bubble filled in.**

A participant who has an abnormal urine dipstick result for any reason may be rescreened ***once*** for eligibility.

If the participant does not return for a repeat urinalysis or if the repeat urinalysis is still positive, the participant is not eligible for PRIDE. Complete a second DIPSTICK URINALYSIS FORM, as necessary, and the Inclusion/Exclusion Checklist if appropriate, marking "Yes" for item D of Exclusion Criteria.

10.3.4 Vital Signs

Measure the participant's blood pressure and pulse using the Dinamap Monitor Pro 100 according to the instructions in Chapter 14.2. Enter the results on the VITAL SIGNS data form.

Uncontrolled hypertension is an exclusion criterion in PRIDE. Blood pressure must be less than 160/100 mmHg, with or without an anti-hypertensive medication, in order for the participant to qualify for the trial. For added safety, if the blood pressure is higher than 140/90 at SV1 the participant should be referred to her health care provider for appropriate treatment. In this case, measure the blood pressure again at SV2 for safety purposes and to confirm that the participant has consulted her physician. **When a repeat BP measurement is made at SV2 a new VITAL SIGNS form must be completed**. Blood pressure must be less than 160/100 at either SV1 or SV2 in order for the participant to meet entry criteria.

If the participant has uncontrolled hypertension (BP equal to or greater than 160/100 at SV1 and SV2) she is not eligible for PRIDE. In this case cancel the remainder of the visit and update the Inclusion/Exclusion checklist, marking

"Yes" for Exclusion Criteria, item H.

10.3.5 Height /Weight

Measure the participant's height and weight according to the directions in Chapter 14.1, Physical Measurements. Record the results on the HEIGHT/WEIGHT data form.

Calculate the Body Mass Index by dividing the weight in kilograms by the square of the height in meters. Round to the nearest whole number and record the result in BMI, item #1. To confirm the calculation, look up the BMI on the chart (Appendix 10B). The two numbers should be very close. (The chart is less precise than the calculation). If they are not, please recheck your measurement and calculations and make any necessary corrections to the data form. The calculated value is the value that determines eligibility.

If the BMI is **less than 25kg/m^2** or **greater than 50kg/m^2** the participant is not eligible. In this case please fill out the Inclusion/Exclusion form, marking "No" for Inclusion criteria, item B.

10.3.6 Health History

The health history is a self-administered questionnaire that should be filled out by the participant during the clinic visit and checked by study staff before the participant leaves the clinic. Review the form for missing responses, for completion of sub-category questions (e.g. if #2 is answered "yes" then 2a should be completed) and for information that affects eligibility. **There are some important exclusion criteria contained in the health history**. An interviewer-annotated version of this form that highlights the eligibility questions is attached as Appendix 10C.

10.3.6.1 Health History Questions

Questions 1 – 4. These are demographic questions only and have no bearing on eligibility. Check for completeness.

Please note that the following questions 5 – 9 do <u>not</u> exclude the participant:

Question 5. Peripheral vascular disease or surgery for PVD does <u>not</u>

exclude the participant.

Question 6. A stroke, cerebral infarction, cerebrovascular accident (CVA) or a transient ischemic attack (TIA) do not exclude the participant, however, the sequelae of these conditions may. The participant is ineligible for the study if she is unable to walk without the use of a cane or walker, or if she cannot read or write well enough to complete the questionnaires and diaries.

Question 9a and 9b. Hysterectomy and removal of the ovaries do not exclude women from PRIDE.

Question 9c. Surgery for prolapse of the bladder, uterus, vagina or rectum does not exclude the participant. A urethral dilation done to relieve pain from repetitive urinary tract infections (cystitis) does not exclude the participant.

Question 10. If the participant has trouble remembering when she started leaking urine continually, help her recall by asking her to think of other significant events or dates that may have occurred around the same time. Alternatively, as a recall prompt, ask her if she was leaking urine when she was 30 or 35 or 40 years of age, etc. Note that, in order to qualify for the study, she should have been leaking urine for 3 months or more at the time of the Eligibility Screening. Please confirm with her that she has been leaking urine for at least 3 months.

Questions 11 – 12. These questions do not affect eligibility. Please check to make sure there is a response for each question.

Question 13. If the "Yes" bubble is marked then either "Yes" or "No" in the side-box must be marked. If the "No" bubble is marked, one or more of the bubbles in the next side-box must be marked. This question does not affect eligibility.

Question 14. This question relates to the economic impact of incontinence and does not affect eligibility. If the response to question 14 is "Yes", questions 14a and 14b must be answered.

Question 15. One or more bubbles must be marked. None of these conditions excludes the participant.

Question 16a - 16g. These questions pertain to physical or neurological problems that may affect incontinence. **A "Yes" response to any one of these questions excludes the participant.**

In this case, mark the Inclusion/Exclusion form as follows: If the participant responds "Yes" to 16a, 16b, 16c, or 16d, then mark "Yes" for Exclusion Criteria, item G. If the participant responds "Yes" to 16e, 16f or 16g, then mark "Yes" for Exclusion Criteria, item E. If the participant marks "don't know" to any of the questions 16a to 16g she is still eligible to continue screening.

Questions 17. This question probes for a history of hypertension. A "yes" response does not exclude the participant. Blood pressure will be measured during screening to determine eligibility.

Question 18. High cholesterol does not exclude the participant.

Question 19. If the participant has a history of coronary heart disease she is not excluded from PRIDE, but she must obtain approval from her health care provider in order to participate in PRIDE. Please confirm that she has obtained a letter and make sure the letter is filed in her study binder prior to the Randomization Visit.

10.3.7 The 7-Day Diet and Exercise Diary

Self-monitoring is a cornerstone of the behavioral intervention and will be encouraged throughout the study in the weight loss group. Participants will be asked to self-monitor dietary intake (foods eaten, portion size, calorie content, and fat grams) and physical activity (including type, duration, and number of steps walked, when applicable) in a seven-day diary that will be provided to them. The ability and willingness to self-monitor is an entry criterion for PRIDE.

At SV1, give the Run-in Food and Exercise Diary to the participant and ask her to record her food and beverage intake and type of exercise each day for 7 days. The number of calories, fat grams and steps taken is *not required* during screening. The diary should be kept for 7 consecutive days. Ask the participant to bring the completed diary with her to her Screening Visit 2.

10.3.8 Take Home Questionnaires

Provide the participant with a packet of the following questionnaires to take home and complete at her leisure. She may also choose to fill them out at the clinic or to start filling them out at the clinic and then take them home. All of these options are acceptable.

Instruct the participant to fill out questionnaires using the same techniques that staff use for Teleforms:

- use a black pen
- make corrections by drawing a line or an X through the wrong bubble, and filling in the correct one
- read the instructions at the top of each page and/or before each question
- fill in the bubbles completely
- participants should not mark anything in the banner of the forms nor make notes or comments on the forms

Ask the participant to bring back the completed questionnaires to the next visit. Provide her with a telephone number and encourage her to call if she doesn't understand the questions or is unsure about how to complete a questionnaire. **If the participant refuses or, in the judgment of the investigator, is incapable of filling out these questionnaires in a reasonably competent manner, she is not eligible to participate in PRIDE**. If this is the case, fill out the Inclusion/Exclusion Checklist by marking the "No" bubble for Inclusion Criteria Item F.

10.3.8.1 Paffenbarger Activity Questionnaire (2 pages)

Most of this questionnaire refers to the previous week's activity level. Question 1 determines if the previous week was an unusual week for the participant. If the answer to this is "Yes", the participant is instructed to choose a different week that was more "usual" when thinking about the response to each question.

Note that question 2 refers to *flights* of steps *per day* as opposed to individual steps and question 3 refers to city blocks walked *per day.* Remind the participant that the activities in question 4 should <u>not</u> include walking since that is recorded in question 3.
Staff may help participants complete this questionnaire as some of the

questions can be confusing.

10.3.8.2 Incontinence Impact Questionnaire (3 pages)

This is the IIQ, not to be confused with the one page 2IQ which has already been completed. The questions on the IIQ assess how much and in what ways urinary incontinence has affected the participant's quality of life. Only one response should be selected for each item.

10.3.8.3 Urogenital Distress Inventory (2 pages)

This questionnaire focuses on specific symptoms the participant may experience. Note that either the "No" or the "Yes" response should be selected for each item. If "Yes' is marked, then one of the next four bubbles should be marked.

10.3.8.4 Health & Activity Form (SF-36) (5 pages)

This is a standardized, quality of life questionnaire. Only one response should be selected for each question.

In general, these questionnaires are self-explanatory with instructions at the beginning of each page or each question. Please contact the Coordinating Center immediately if you notice that a question is constantly misinterpreted. The FFQ is more complicated and is described in more detail below.

10.3.8.5 Food Frequency Questionnaire

The PRIDE Food Frequency Questionnaire facilitates analysis of specific nutrients as well as overall dietary patterns. It is designed to be sensitive to dietary changes that are likely with the planned intervention. In addition, the opportunity to analyze and contrast dietary intake across and within intervention and control groups is likely to increase our understanding of how differences in food and beverage intake affect women with urinary incontinence, with or without weight loss.

The PRIDE FFQ is a modified Block Dietary Data Systems questionnaire. It is self-administered with limited staff support. Project

staff will provide basic instructions for completing the form and will review the form upon its return.

Here are a few reminders to help with data quality:

No other marks on the questionnaire	Comments or notes should not be written on the questionnaire as they may interfere with scanning. Comments can be made on a separate page.
Bubble completely	Fill in the answer bubbles completely. Do not simply make a checkmark or an 'X' over the bubble.
One bubble per answer	Choose only one response in each section.
No staples	Avoid using staples on the form since they must be removed prior to faxing. Marks left by staples can interfere with Teleform's tracking, form number or page number codes.
No extra pages	Do not add any extra pages or papers with notes on them when faxing the form. Do not attach yellow stickies. Teleform reads only pre-defined boxes.
No folds	Do not fold the questionnaire as this can interfere with faxing and interpretation.
No 3-hole punch	Holes might interfere with the reading process.

A clear, positive introduction and explanation of the questionnaire is extremely important to obtain valid information and to help the participant complete the form with minimal frustration.

Although portion size improves the accuracy of the nutrient estimates, the reviewer should be aware that frequency of consumption is more important than exact portion size in determining long-term usual intake. Show the participant the first few pages of the questionnaire and point

out the headings that appear on each page referring to frequency and portion size. Be sure to give the participant the photograph page (500 copies will be provided to each site) that illustrates approximate portion sizes.

To help orient participants to the form, tell them that the items are grouped by type of food (e.g., fruits, vegetables, meats). Encourage her to glance through all the different itemized food in each category before she starts to fill out the form. Remind participants to think of foods eaten both at home and away from home. Remind them to include both meals and snacks. If participants do not prepare the food themselves, ask that they answer to the best of their ability. If the participant uses an item with a frequency that does not fit exactly into one of the available ranges, ask her to choose the closest category.

The **time frame** that the FFQ covers is "the past 6 months or so". This is deliberately a little vague because no one is expected to remember exactly what was eaten during the past 6 months. The idea is to get a usual pattern of frequency. Some respondents may comment, "Oh, I can't even remember what I ate yesterday!" It's important to make clear to participants that the idea is not to be precise, but to think about their usual pattern. For example, they don't have to remember how many times they had eggs in the past 6 months. Instead, what they can recall with reasonable accuracy is, " I have eggs about twice a week."

The participant may indicate that she has changed her habits in the past 6months. If the change is recent ask her to report her former pattern of eating. If the change has been well incorporated and appears to be lasting and stable, she should report on the new pattern rather than the former pattern.

Emphasize completeness and that no line should remain blank. The participant should check “Never” rather than simply skip foods she rarely or never eats. Inform participants that if they don’t eat a particular food, they may leave the serving size blank.

The food list represents the most important nutrient sources in most people's diets. It does not and is not intended to include all possible foods that people ever eat. Thus, it is likely that some foods that a person eats will not be on the list. Do not attempt to force unmentioned

foods into categories by guessing at their similarity.

Here are some clarifications:

Fruits

In this section, the number of times per month or week refers to number of days per month or week. For example, the respondent eats bananas on about two days a week. Then, the portion size section provides the location where the respondent can record how many pieces of that fruit she eats, on the days she eats them.

Seasonality: Among the fruits, all but one of the items refer to food intake year round. If any of these "year-round" foods are eaten more in one season than another, ask respondent for her best estimate of a year-round average.

Jams and jellies should not be counted as servings of fruit. Fruit in yogurt does not count as servings of fruit.

Bananas	All kinds, all sizes. The frequency section means "how often", not how many bananas per week. Show the participant that she should record how often first; then in "portion size" she documents "how many" on each occasion.
Fresh apples or pears	All kinds, all sizes; includes Asian pears. Discourage respondents from trying to do math, adding up separately their apples and their pears. An average is fine.
Oranges, tangerines, not including juice	All kinds, all sizes; includes tangerines, tangelos, mandarin oranges. (Orange juice is a later item.) If respondent only uses oranges to make juice, tell her to wait and count that as orange juice. And then use the glasses for portion size. If she sometimes eats them as oranges and sometimes as juice, ask her to estimate the frequency of 'as

	oranges' in the fruit section, and then later the frequency of 'as juice' in the juice section.
Grapefruit, not including juice	All kinds, all sizes.
Cantaloupe	The focus here is on cantaloupe. Other melons should be counted only if they are deep orange like cantaloupe. Do not include honeydew or other non-orange melons.
Raw peaches, apricots, nectarines, in season Applesauce, fruit cocktail, canned pears	Any type. Report frequency only for the few months when they are "in season". Frequency is average year-round frequency of consumption. Do not include canned peaches, apricots, plums, etc.
Canned, frozen or stewed peaches or apricots	Any type. Frequency is average year-round frequency of consumption.
Any other fruit...	Any fruit, canned or fresh. Year-round frequency.
<u>Breakfast items, dairy</u>	
Eggs, including biscuit sandwiches and Egg McMuffins	Includes real eggs when eaten as eggs, including scrambled, boiled, fried, or on sandwiches, deviled, egg salad or quiche. Do not count eggs used in cooking, such as in cakes, custards, etc. Do not count Egg Beaters, egg substitutes, or only egg whites.
Bacon	Bacon when eaten at any time, including in sandwiches.
Breakfast sausage, including sausage biscuits	This includes breakfast-type items, but not cold-cuts for sandwiches, not main-meal items like Italian or Polish sausage, and not hot-dog type sausages like German hot dogs.

	Turkey sausage should be included here.
Pancakes, waffles, French toast	With or without butter or syrup.
Cooked cereals like oatmeal, cream of wheat or grits	This refers to all cooked cereals, including cream of rice, and less common types like kasha.
Any kind of cold cereal	This is a general question about all kinds of cold cereals. The next three questions ask about specific types of cereals, however, it is not necessary to make the sum of the three types of specific cereals add up to this first general question.
Fiber or bran cereals	This includes the very-high-fiber cereals like All-Bran and the moderately high-fiber cereals like "Fruit-n-Fiber". Any cereal with the words "bran" or "fiber" in their titles may be included here. Note that the cereals should be counted even if they are eaten as a snack rather than a breakfast cereal, and regardless of whether they are eaten with milk.
Product 19, Just Right or Total	This item includes only these three cereals. These cereals contain 100% of the RDA (Recommended Dietary Allowance) for several nutrients.
Other cold cereals	This item refers to all other cold cereals, like corn flakes, rice krispies, Special K, or sweetened cereals like Frosted Flakes, etc.
Milk on cereal	This is relevant only if cereal is eaten. Otherwise, the answer is “Never”.
Cottage cheese	Includes all varieties, regular or low-fat, farmer cheese or ricotta.

Other cheeses	Includes all types, regular or low-fat, hard cheese or soft cheese, natural or processed, including cream cheese. This category should not include cheese eaten in lasagna, pizza, etc.
When you eat cheese, ...	"Cheese" here refers specifically to cheese by itself, not as part of pizza, lasagna, etc.
Yogurt, frozen yogurt	Includes all varieties, with or without fruit, regular or low-fat, sweetened or artificially sweetened. Do not count the fruit in yogurt separately as fruit.
French fries and fried potatoes	Includes home cooked or restaurant fries, and "home fries".
White potatoes not fried...	Includes all forms of potatoes except fried. Do not include potatoes eaten in soups or stews, as those are captured elsewhere.
Sweet potatoes, yams	All types.
Rice, or dishes ...	This includes fried rice, Rice-a-roni, beans-n-rice, rice pudding, etc.
Stuffing or dressing	Bread or rice stuffing, or stovetop stuffing
Baked beans, chili with beans....	This includes all dried-type beans such as navy beans, red beans, etc. Bean, lentil or split pea soups may be counted here.
Corn	Fresh, frozen or canned. One ear of corn equals approximately a "B" or medium serving**.**
Green beans or green peas	Green beans include canned, frozen, fresh, or in salad bars. Green peas refers to canned, frozen, fresh, or in salad bars, but not to dried-type peas like black-eye peas, split

	peas.
Broccoli, cauliflower	Includes cooked or raw. Includes items from salads only if the amount comes to at least the size of a half-cup, and then only the frequency with which this vegetable itself is eaten, not the frequency that salad may be eaten.
Carrots, or mixed vegetables containing carrots...	Includes cooked or raw. Include items from salads only if the amount comes to at least the size of a half-cup.
Spinach	Includes cooked or raw. Spinach salad should be recorded here, not under salad.
Collards, mustard greens, turnip greens	This refers specifically to the dark-green, strong-flavored greens. Beet greens, for example, may be counted here. However, lighter-green leafy vegetables such as celery tops should not be counted here.
Cole slaw, cabbage etc.	Includes raw or cooked cabbage, including Chinese cabbage, and cole slaw whether homemade or from a restaurant.
Green salad	Includes all kinds of green salad that include some lettuce, whether mostly of iceberg lettuce or of other types of lettuce, and regardless of whether other vegetables are sometimes eaten in it. Spinach salad should be recorded under "spinach", and should not be double-counted here.
Raw tomatoes	Includes tomatoes eaten alone or in salad. Does not include tomato sauces, which are captured under 'spaghetti', etc. Does not include the tomatoes in tomato or vegetable soups, which are captured under that item.

Salad dressing	All types, creamy or not, including oil & vinegar.
Any other vegetable...	Includes any vegetable not already mentioned.
Vegetable soups...	Any type of vegetable soup that has a lot of carrots, or has a tomato base.
Other soups...	This is the catch-all for all other forms of soup, whether creamed or not, including "instant" soups.

Meats and main dishes

Hamburgers, cheeseburger, meat loaf...	All sizes, at home or in a restaurant. Does not include the ground beef used in spaghetti, lasagna or pizza. Only hamburgers, etc. made with beef are to be included here. Turkey burger should not be coded here, but should be included under "chicken or turkey, roasted or broiled".
Beef including steaks, ...	Do not include beef eaten as ground beef.
Liver...	All forms.
Pork...	Do not include pork-based lunch meats.
Mixed dishes with meat...	Include any mixed dish with beef, pork, veal or lamb. Do not include beef stew reported earlier for the "carrots" item. Do not include mixed dishes with chicken.
Fried chicken...	All parts of a chicken are included (wings, thighs, breast, etc.) provided they are fried. Include McNuggets, etc.
Chicken or turkey...	Include turkey burgers here, but not chicken/turkey eaten as part of a mixed dish.

Chicken stew...	Includes any mixed dish with chicken.
Shellfish...	All forms, including clams, mussels, squid, oysters.
Tuna...	All forms of tuna except raw as sushi, light meat or dark, in oil or in water, straight or in a casserole. Portion size, however, refers to the amount of tuna, and should not include any noodles, etc., eaten with it.
Fried fish...	Home-fried, restaurant, fast food. All types of fish.
Other fish...	All other fish, after excluding fried, tuna or shellfish. Include fish eaten raw.
Hot dogs	All forms, including chicken/turkey.
Bologna...	Lunch meats, all types. Ham refers to slices for sandwiches; ham eaten as a roast or as the entree for a main meal should be reported under "pork". Do not include small amounts eaten on pizza, etc.
Spaghetti... with tomato sauce	This item should include only those pasta dishes that are eaten with tomato sauce. It can include mixed pasta items such as raviolis.
Cheese dishes <u>without</u> tomato sauce...	This item should <u>not</u> include any pasta dishes that are eaten with tomato sauce. This includes only dishes that commonly have a fair amount of cheese, such as macaroni and cheese, certain Mexican dishes that have a lot of cheese, Welsh rarebit, etc. Incidental sprinkle cheese often used on spaghetti does not make it count as a cheese dish. Cheese

sandwiches should be counted in the earlier 'cheese' item, where number of slices can be indicated.

Pizza... All forms, all sizes, all toppings.

Breads, snacks, etc.

Point out to the participant the change in the frequency categories for this section. Never and "Less than once a month" are combined and there is an additional category "2 or more times per day".
If the participant eats bread "twice per day", but has a different portion size each time, she may have difficulty coding her consumption correctly. In this case you can suggest she convert her frequency of consumption to "every day", and then code the portion size as the total number of pieces consumed each day. For example, if the participant eats two slices of bread for lunch and one slice of bread for dinner, you may code this as "Every day", and "3 slices".

Biscuits, muffins... Biscuits include homemade or from fast food places such as Kentucky Fried Chicken, McDonalds. Muffins include bran muffins, blueberry muffins, etc., but do not include English muffins, which should be included under 'Rolls,...', below.

Rolls, Hamburger buns, English muffins, ... All types, all sizes. Note that these items come as two halves. Therefore, if they only eat 1/2 a bagel, etc., the portion size should be marked as "1/2". Only a whole bagel, English muffin, hamburger bun, etc., should be marked as "1".

White bread... White, French, Italian, etc., all forms. In reporting portion size, the response is in "slices".

Whole wheat... Includes rye, pumpernickel, or other dark breads.

Cornbread...	Includes cornbread, corn muffins, corn tortillas, hush puppies.
Butter or margarine...	All forms, on bread or added to vegetables at the table. A "pat" is about one teaspoonful.
Mayonnaise...	Include all mayonnaise-type spreads.
Peanut butter	Other nut butters may also be included in this item.
Ketchup or salsa	All kinds of tomato-based condiments.
Gravy	Include meat gravies or packaged varieties.
Snacks, like potato chips...	Includes low-salt or low-fat varieties of chips. Does not include air-popped popcorn.
Peanuts, pecans...	Any nuts or seeds such as sunflower.
Crackers	Saltines, or any other crackers
Doughnuts, Danish pastry	This is intended to capture full-fat types of doughnuts and pastries. If they eat a low-fat kind of pastry such as Entenmann's coffee cake, they should report it in the next item.
Cakes, sweet rolls...	All kinds of cakes or coffee cakes, home-made or packaged, including snack cakes.
Cookies	All kinds, all sizes.
Ice cream...	All forms including ice cream bars, fast-food milkshakes, etc.
Pumpkin pie...	Include pies or puddings made with pumpkin or sweet potato. However, do not count sweet potato if it was reported as an earlier item.

Any other pies...	All forms, fruit-filled or not. Include fast-food pies.
Pudding	All kinds, including canned, ready-to-eat, and those prepared from dry mix.
Chocolate candy, candy bars	Only chocolate-covered or chocolate-based candy and candy bars should be included here. The point is the chocolate, not just any candy.

10.3.8.6 Beverages and Summary Questions

Point out to the participant another change in frequency categories. First they will mark how often they drink the itemized beverage, and then mark how many glasses each time. A glass is approximately 8 ounces.

Certain responses in the frequency section are blanked out, because they are extremely improbable and would yield substantial overestimates of some nutrients.

Orange juice or grapefruit juice	Canned, frozen or fresh. Do <u>not</u> include fruit-based <u>drinks</u>, or any drink that is not 100% orange or grapefruit juice. (Sunny Delight is not 100% juice.)
When you drink orange juice...	The program will use the answer to this question to choose the type of orange juice to use for the frequency of orange juice reported above.
Hi-C, Kool-Aid, added vitamin C	Include any drinks, whether real fruit juice or not, if they contain added vitamin C. Most forms of Kool-Aid do now contain added vitamin C. Include Sunny Delight here.
Tomato or V8 juice	Any tomato juice, including Clamato, etc.
Other fruit juices, ...	Canned, bottled, frozen or fresh. Other 100%

	real fruit juices (not 'drinks') could be included here, such as lemonade.
Instant breakfast... Ensure...	Include any meal supplement or replacement, such as Boost or Ensure; any type of dieting milkshake, such as Sego or Slim-Fast; or Instant Breakfast milkshakes like Carnation.
Glasses of milk...	This applies to glasses of milk, not to milk added to coffee or cereal, nor to milk added to Carnation Instant Breakfast.
When you drink...	This response applies to glasses of milk, not to milk added to coffee or cereal. If the participant drinks more than one type of milk, ask her to choose the one she drinks most often.
Regular soft drinks...	Any soft drink that is not artificially sweetened. Includes cola, ginger ale, pepper types, orange or grape soda, etc., or sugar-sweetened bottled water. If the participant buys large bottles of soft drink (such as the standard 64 oz. bottle) and then drinks it in cups or glasses she can estimate the portion size that she drinks each time.
Beer	Bottles, glasses, cans, or draft, all varieties. Do not include nonalcoholic beer, here but include it in the open-ended section at the end of the questionnaire.
Wine...	All forms, including champagne, spritzers. Include nonalcoholic wine in the open-ended section at the end of the questionnaire.
Liquor...	Include all forms, including whisky, scotch, gin, etc. Note here that a standard portion size will be assumed.

Coffee...	Include caffeinated or decaffeinated, brewed or instant.
Tea...	Any form of regular tea or iced tea. Do <u>not</u> include herbal teas.
Cream, half and half...	This includes half-and-half or creamer, but <u>not</u> milk. Includes liquid or powder varieties of creamer.
Milk in coffee or tea	Regardless of type of milk.
Sugar or honey	Refers to only real sugar or honey, not sugar substitutes.
Servings of vegetables, fruit	For example: green beans with lunch and squash with dinner would be 2/day; green beans with lunch and green beans with dinner would be 2/day; nothing with lunch and both squash and green beans with dinner would be 2/day. This does not mean 'how many different kinds'; does not refer to 'seconds'; and excludes mainly-lettuce salads. (See below for more on salads.)

Answers to participant questions:

Q: "Do you mean different <u>kinds</u> of vegetables (fruits, breads)?"
A: "**No, just <u>how often</u> you eat vegetables of any kind**."

Q: "Should I count second helpings as two servings?"
A: "**No, this is just <u>how often</u> you eat vegetables of any kind**."

Q: "Give me an example of how to count them up."
A: Fruits: "**If you usually have some fruit with breakfast and some fruit for a snack, that would be twice a day**."
A: Vegetables: "**Green beans with lunch and squash with dinner: 2/day; green beans with lunch and green beans with dinner: 2/day; nothing with lunch and both squash and green beans with dinner: 2/day**."

Q: "What if I have a big salad with lots of stuff in it?"
A: If you usually have ½ cup (size "B") of any single vegetable such as broccoli in the salad, count that vegetable as a serving of vegetables in this "general question".

Frequency of fat or oil in cooking	Note that fat or oil use in fry, stir fry, simmer or season. It does not include fat used in baking; does not include oil used on salad; and does not include butter/margarine used on bread.

10.3.9 Scheduling SV2

Schedule Screening Visit 2 at least 8 days after SV1 to allow time for the completion of the Food and Exercise Diary. The participant should be given the following items to take home:

- Run-in Food and Exercise Diary
- Paffenbarger Activity Questionnaire
- Incontinence Impact Questionnaire
- Urogenital Distress Inventory
- Health & Activity Form (SF-36)
- Food Frequency Questionnaire
- a reminder to bring all her prescription and non-prescription medications to the next visit.

10.4 SCREENING VISIT 2 (SV2)

10.4.1 Preparation for SV2

SV2 is the participant's second individual clinic visit. Call to remind her about the appointment time, length of time it will take and to bring with her all her prescription and regularly used non-prescription medications, the completed questionnaires and the food and exercise diary. Check the Screening Checklist for the forms and diaries you expect at this visit.
Print out the SV2 packet of data forms from the PRIDE website. (Any form or questionnaire with "SV" as a visit box choice can be done at either SV1 or SV2.) Items below that are marked with an asterisk are important for eligibility.

Forms/Procedures Required During SV2

- Review completed take-home questionnaires
- Review 7-Day Food and Exercise Diary*
- Medications Form*
- Beck Inventory*
- Bowel Habits
- Sexual Function
- Sleep Questionnaire
- 2nd 7-day Voiding Diary
- Explain and give 24-Hr Pad Test Kit
- Informed Consent/HIPPA for UDS/other Sub-studies
- Update Inclusion/Exclusion Form*
- Update the Screening Checklist
- Participant Tracking Log (to be updated)

10.4.2 SV2 Procedures

10.4.2.1 Review of Self-Administered Questionnaires

Collect all the self-administered questionnaires from the participant and:

- review each carefully before she leaves the visit
- ask the participant if there were any questions she was unable to answer or any that needed clarification.
- check to make sure that all bubbles are filled in where necessary, and that any errors have been crossed out. If an error has been made and crossed out, it may be necessary for you to circle the correct answer, initial and date your circle. This will clarify for the verifier at the Coordinating Center, which answer is to be accepted to the database.

A careful review at the time of the visit can help avoid queries or possibly a telephone call to the participant for clarification of her responses.

10.4.2.2 Review of the 7-Day Food and Exercise Diary

Collect and review the 7-Day Food and Exercise Diary to make sure the participant is capable of self-monitoring. The diary must be available

and must be completed to the satisfaction of the study interventionist in order for the participant to be eligible for the study.

At this time the interventionist will interview the participant to assess her potential for adherence to the study intervention. These are examples of the components of an eligibility assessment:

- ask what a typical week is like for the participant in an effort to assess availability (with jobs, family, church or community issues) for the program and/or dependency for her time from others.
- ask about distance from the clinic and transportation issues. Participants living more than an hour away from the clinic tend to drop out or reduce visits earlier than those living closer in.
- ask about past behaviors with dieting/exercise…probing their experiences, what they are expecting from the program, understanding randomization and being committed to seeing the program to the end.

The interventionist must agree that the participant is an appropriate candidate for the study before she is randomized. If the participant has not completed the diary satisfactorily, or, if, in the opinion of the interventionist, she is unlikely to adhere to the study protocol, she is not eligible. In this case, fill in the "No" response for the Inclusion Criteria item D and/or the "Yes" response for Exclusion Criteria I on the Inclusion/Exclusion Checklist.

10.4.2.3 Medications Form

At SV1 the participant was asked to bring all her prescription and non-prescription medications to Screening Visit 2. Look at each medication and record either the trade name (preferably) or the generic name of each medication, but not both. Record over the counter medications only if they are taken on a regular basis.

If the participant is not taking any medications regularly, print "NONE" in the boxes after "1. Trade Name."

The following medications may affect weight or incontinence. If the participant is taking any of these medications she is **not eligible** for PRIDE, and you should update the Inclusion/Exclusion Checklist by

marking "Yes" for Exclusion Criteria, A:

Steroids:
Azium (dexamethasone)
Cortisone
Medrol (methyl prednisolone)

For Weight Loss:
Meridia (Sibutramine)
Xenical (Orlistat)
Phentermine: alternate spelling is phenteramine (Adipex-P, Fastin, Ionamin, Obenix, Obephen, Oby-Cap, Oby-Trim, Panshape M, Phentercot, Phentride, Pro-Fast HS, Pro-Fast SA, Pro-Fast SR, Teramine, Zantryl

Prednisolone
Prednisone or Deltasone

For Diabetes:
Amaryl (glimepiride)
Glucotrol (glipizide)
Glucovance (glyburide + metformin)
Glynase (glyburide SR)
Insulin (Humalog, Novolog, NPH, Lente, Ultralente, Lantus, Humulin, Novolin, Novolog, or Humalog)

For Incontinence:
*Ascendin (amoxipine)
Bentyl, Bentylol, Antispas (dicyclomine)
Detrol or Detrol LA (tolterodine)
Ditropan, Ditropan XL, Oxytrol patch (oxybutinin)
Duloxetine (cymbalta)
*Elavil, Endep (amitriptyline)
Levsin, Levbid, Anaspaz, Urised, NuLev,
Cystospaz (hycoscyamine)
*Pamelor, Aventyl (Nortryptyline)
Pro-Banthine (probantheline)
Prosed/DS
*Tofranil (imipramine)
Urised
Urispas (flavoxate)

*If the medications with an asterisk are prescribed for depression the

participant may continue with the screening process. A query will be generated by the data-system if any medication on this list is entered into the database for a participant that is randomized. When the medication is used for depression you may address the query as "not an error".

10.4.2.4 Beck Depression Inventory (4 pages)

This questionnaire should be completed by the participant during the clinic visit and should be reviewed by a PRIDE staff member before the participant goes home.

Only one bubble should be selected for each question. There are 21 questions (A to U), with four possible responses to each question, listed in the order of feeling best to feeling worst. Responses are scored on a scale of 0 – 3, with 0 being the first listed response (not depressed) and 3 being the last listed response (most depressed). The questionnaire should be reviewed during the clinic visit while the participant is otherwise occupied.

A participant with a total depression score ≥ 24 on the BECK INVENTORY may be depressed, and careful consideration should be given as to whether participation in PRIDE is appropriate for her. The participant should be told she might be depressed, and referred to her health care provider for evaluation. If the response to question "I" on the BECK INVENTORY, about suicide intent, is the third or fourth response listed, (i.e "I would like to kill myself" or "I would kill myself if I had the chance") she should be evaluated immediately by a qualified psychiatric clinician.

If it is felt that this woman is not an appropriate candidate for PRIDE, update the Inclusion/Exclusion checklist by marking "Yes" for Exclusion Criteria I.

10.4.2.5 Bowel Habits Questionnaire (4 pages)

This questionnaire may be completed at the clinic during SV2 or may be taken home and returned at the Randomization Visit. The questions ask for the participant's experiences using the past 3 months as a general reference period.

Question 1: asks for the total number of bowel movements in *one week*.

Question 2: asks for the typical length of time the participant sits on the toilet on *each occasion*.

Question 3: Only answer 3a and 3b if the response "Formed" has been selected.

Question 4: **A – F**: Only one response per item is allowed.

Question 5: A – H: Only one response per item is allowed.

Questions 6, 7, 8 and 9: Only one response per question is allowed.

Question 10 A – D: Only one response per item is allowed.

10.4.2.6 Sexual Function Questionnaire (4 pages)

Some participants may feel uncomfortable answering this questionnaire if they think that staff can look at their responses. Therefore, each participant should be given an opaque envelope in which to place the questionnaire when she is finished. To maintain participant anonymity, the envelope will be addressed to the Coordinating Center (CC) and can be mailed by the participant or returned sealed to the Study Coordinator for mailing. A Coordinating Center staff member will open each envelope and fax the questionnaire to the Teleform data system. Queries will not be posted for this form. In some cases data may be irretrievable.

10.4.2.7 Sleep Questionnaire (4 pages)

Excessive weight has been correlated with poor sleep quality but frequent urination may also disturb sleep.
Questions 1 and 3: Remind the participant to fill in the bubbles for a.m. OR p.m., not both.
Questions 4 and 5: Round ¼ hour back to the nearest hour. Round ½ and ¾ hrs up to the next hour.

10.4.2.8 The 24-Hour Pad Test

10.4.2.8.1 Background and General Description

Pad testing is used to quantify the amount of urine lost involuntarily. This test, standardized by the International Continence Society, correlates well with UI symptoms and has proven reproducibility.

The pad test is completed for one complete 24-hour period starting at the participant's waking time and ending **exactly** 24 hours later. It should be done during the time that the second Voiding Diary is kept, ideally, during days 4 – 7 of the 7-day Voiding Diary.

Participants should avoid doing this test during their menstrual period or when they have diarrhea because it is impossible to separate the weight of blood or stool on a pad from the weight of the urine. We understand that it may be difficult for PRIDE participants to predict these events, but every effort should be made to avoid such times to complete the Pad test. For similar reasons, participants should avoid intercourse as well as the use of vaginal creams, jellies, suppositories or douche treatments during the conduct of this measure. Finally, since some women have reported that tampon use reduces the number of urinary accidents they have, ask participants to avoid the use of tampons while completing the Pad Test, whether they are menstruating or not. The Pad Test should be done on a typical weekday when normal or typical daily activities occur. In other words, we do not want participants to avoid certain days of the week or to change activities that would usually cause them to have urinary accidents; we want measurements from a typical day.

Participants with pelvic organ prolapse should complete the measures in their "typical" state. If the participant usually wears a pessary, then a pessary should be worn during the conduct of the Voiding Diary and Pad Test.

Participants will be asked to self-report the presence of blood or

stool on each pad and the study nurse will document contamination on the data form.

Finally, it is best if participants complete the Pad Test one or two days before the next scheduled study visit. In general, participants will see the merits of this rule, as it limits the number of days they have to hold onto 'used' pads. More importantly for our purposes, it minimizes the potential for urine evaporation from the "used" pads. Third, the shorter the time period between completion of the Pad Test and the date of the study visit, the less likely it is that participants will forget to bring the used pads to the visit. If scheduling is difficult, the clinical site can supply the participant with an overnight, pre-addressed mailer and she can mail back the used and unused pads within a day or two of completing the Pad Test.

Please note that if the participant loses her diary or has to repeat the diary for any reason, she will have to repeat the Pad Test also.

To summarize instructions for participants (Appendix 10D):

- Complete the Pad Test in a continuous 24 hour period between days 4 to 7 of the Voiding Diary days. Thus, the 7-day voiding diary should begin at least 8 days before the next scheduled visit. The pads should be returned at the time of the visit or can be mailed back in a mailer supplied by the site;
- Avoid the use of vaginal creams, jellies, suppositories or douche treatments during the conduct of the measures;
- Do not use tampons while completing the Pad Test, whether you are menstruating or not; and,
- Avoid having intercourse while completing the Pad Test.
- Complete the measures in your "typical" state (with or without a pessary)
- Mark on the Pad Test Sticker the presence of blood or stool on individual pads

In light of all of these essential restrictions, it is best if the study nurse works with the participant to schedule the date of the next study visit and select the actual days for completion of the

Voiding Diary and Pad Test using a calendar as reference.

10.4.2.8.2 Materials/Space/Equipment for Pad Test

- Instructional slide presentation for the 7-Day Voiding Diary and the 24-Hour Pad Test
- A screen and computer hook-up
- A private room for viewing the instructional slides
- A 7-Day Voiding Diary with the participant ID and acrostic entered
- The Pad Test Reminder insert including instructions for participants and a reminder of the Pad Test start date
- A Pad Test Kit including the estimated number of Poise™ protective pads (extra) each placed inside a 6″ x 9″ Zip-lock biohazard bag; one bag for each pad
- A larger plastic bag for all the Kit materials
- Pad Test labels, one pre-printed with the participant's confidential ID number, spaces for the pad number and the gram weight before use, and the other pre-printed with contamination options for the participant to check: two labels per pad ***(Avery Label 1″ x 2⅝″, # 5260)***
- A calendar as reference to select the dates/days for completing the Voiding Diary and the Pad Test and for scheduling the next study visit
- Standard scale for weighing each pad before and after use: Denver Instrument* XP -300 Portable Electronic Toploader Scale: 115V 50/60Hz XP-300 300g Balance, 0.01g Readability, Automatic Calibration, Stainless-Steel Weighing Pan, 208L x 211W x 69mmH . This scale (balance) is a study-required piece of equipment.
- Stapler

10.4.2.8.3 Care and Calibration of the Scale

Care and maintenance of the scale is important to maximize the accuracy of the Pad Test. A scale that is accurate to .01 gram has been selected to maximize precision for this outcome measure. A complete manual is included with the scale you purchase.

The scale should be kept on a stable surface, protected from

jarring or movement, and used only for weighing the pads for PRIDE. The scale is self-calibrating but two standard gram weights (for example, 20 and 100 grams) should be utilized to check accuracy once a month. A calibration log should be kept for quality control purposes (Appendix 10E).

10.4.2.8.4 Preparing the Pad Test Kit

The following steps are listed in logical sequence:

1. First, determine the number of pads needed for the 24-hour test. Show the participant the type of pad you will give her and ask her how many of these pads she would expect to use if the day selected were to be one of her worst. Include one and a half that specified amount of pads in the kit you prepare for her. Some participants may report that "*Poise Extra*" pads are insufficient to manage their incontinence. These participants are permitted to complete the Pad Test using an alternative product appropriate to their incontinence needs. If this situation occurs, request that the participant bring in a sufficient number (1½ times the amount needed on one of her worst days) of the alternative product for pre-weight measurements. Then, proceed to follow all other weighing guidelines listed below. If an alternative pad is used, please notify the Coordinating Center.
2. Next, make arrangements for the participant to watch the instructional slides somewhere in the clinical site. The slides last 5 minutes.
3. While the participant watches the slides, the study nurse should prepare the participant's Pad Test Kit making certain that all of the pads are weighed and labeled correctly.
4. Using clean technique (wash hands, wear clean gloves, work in a clean field) remove the commercial outer wrapper of the pad(s).
5. Fold the pad gently and place each pad in a regulation biohazard zip-lock bag and seal the bag.
6. **Then, staple the bag at the top, above the bag's zip-lock seal. Remember to staple the bag prior to weighing the pad. Since most pads will be returned with the staple still attached to the bags, the staple is included in the pre-weight**

measure. Therefore, the weight recorded on the label will now include the weight of the staple.

7. Next, weigh each single pad in its biohazard bag following the weighing procedures described in Appendix 10F. Don't forget to fold up the biohazard bag to be certain that no part of the bag falls off the weighing pan or touches any area of the scale other than the weighing pan. The weight can vary significantly if this occurs.
8. Hand-write the weight of the pad (in gram weight to the .01 measure) on the appropriate label and stick the label on the outside of the biohazard bag. It is important to always weigh the pad in the biohazard bag without any label(s) attached.

This much of the procedure can be completed in advance in batches for many pads. A record must be kept of the date when the batch pre-weighing was done and pads must be used within six months of the pre-weighing.

9. When you prepare the personalized Pad Test Kit for the participant, first enter the participant's ID number and acrostic on as many labels as pads needed; then enter a sequential pad # in the space provided. For example, if you are giving the participant 6 pads you will write a number "**1**" on the first ID label, a number "**2**" on the second ID label, a number "**3**" on the third ID label and so on, until you have 6 confidential ID labels each with a pad # written on the label. Then, place these labels on the outside of each of the biohazard bags included in the participant's Kit. Now each biohazard bag will contain a clean pad and will have two labels showing the participant's ID and acrostic, pad #, pre-use gram weight and contamination categories.

NOTE: The weight of the two study specific "Avery" labels is equal to the weight of one pad adhesive paper that the participant will remove and discard when she uses the pad. Therefore, when a used pad is returned and reweighed only the weight of the urine loss will be measured.

10. Complete items 1 through 4 of the Pad Test data form. The pre-weight values for each of the pads included in the

participants Pad Test Kit must be recorded on the form before you give the Kit to the participant. (If you dispense more than 10 pads you will need to use a Pad Test Auxiliary form as well.) The rest of the form will be completed when the participant returns the Kit. You may use pads from more than one pre-weighing batch as long as no pre-weighed pad has been kept longer than 6 months. When using pads from more than one pre-weight batch enter the date (#3 on the Pad Test form) that the majority of pads were pre-weighed.

11. Finally, put all of the bags with pads into a larger plastic bag that the participant can carry easily and discreetly.

10.4.2.8.5 Completing the Measures

1. When the participant finishes viewing the slides study personnel should meet with her to review the instructions and answer any procedural questions she might have regarding either the Voiding Diary or the Pad Test.
2. Then, using the participant's calendar, identify the time of her next menstrual period and determine the appropriate dates and days to complete the Voiding Diary, the Pad Test, and next study visit. Write the start day of the diary and the start day of the Pad Test on the Pad Test Reminder insert and place it in the Pad Test Kit. Review the contents of the Kit with the participant.
3. Next, the study nurse gives the participant the Pad Test Kit, prepared to the participant's personal specifications and gives the participant the clinic telephone number, encouraging her to call with any question or concerns.
4. As a reminder, the study nurse should make arrangements to contact the participant one day prior to the start of the Voiding Diary to remind her to complete the Diary and Pad Test as planned. The nurse should schedule with the participant a convenient time to talk for the reminder call. This will provide a good opportunity for the nurse to answer any final questions the participant might have prior to the start of the measures.

10.4.2.8.6 Recording the Data

When the participant returns with the completed Voiding Diary and the Pad Test Kit (including all used and unused pads) the study nurse weighs each of the Pads in the Kit per protocol and completes all the remaining sections of the Pad Test data form at that time (see Chapter 12, Randomization Visit).

10.4.2.8.7 Pad Test Form

The person who distributes the Pad Test Kit must be PRIDE-certified. This should be the same person who completes the participant education procedures for the Pad Test including slide viewing, a review of the participant's Pad Test Kit materials and at-home participant procedures after slide viewing, completing the follow-up phone contact, etc.

1. **Date Pad Test Kit distributed:** Record the date you complete the participant education procedures and give the Pad Test Kit to the participant.

2. **Number of Pads in the Kit:** Record the total number of pads included in this participant's Pad Test Kit.

3. **Date pre-weights are recorded:** Record the date when the pre-weight measurements were done. Note that this is usually before the date of the visit.

4. **Pad #:** Record in sequential order, the number assigned to each pad included in the Kit. If 4 pads are included in the kit, record the number 1 in the field A, record the number 2 in the field B and so on. **Pre-weight:** Weigh each Pad following procedures described in Appendix 10F. For each pad included in the Kit, record the pad weight in grams to the nearest .01-gram weight.

No other data can be recorded until the participant returns with the Pad Test Kit and the Voiding Diary.

5. **Date post-weights are recorded:** Record the date when post-

weight measurements are documented on the Data Form.

6. **Post-weight:** Weigh each used pad following procedures described in Appendix 10F. Record the pad weight in grams to the .01-gram weight.

7. **Contamination Code:** Review the Pad Test Record Sheet and confirm with the participant to determine and record a contamination code.

8. **Other codes**: Do not weigh unused pads; leave the gram weight boxes blank.
   - If the pad is missing but not used, according to the participant, leave the gram weight boxes blank and enter "10" as the contamination code.
   - If the pad was returned but not used, enter "11" as the contamination code for that pad.
   - **If the pad is missing and the participant reports that she *did* use it, the test is invalid and should be repeated.** It is very important that all used pads be weighed. In this case, do not complete or fax this form; write "Invalid Test" across the form and file it in the participant's binder. Prepare another Pad Test Kit for the participant and print out a new Pad Test form. When a pad is missing but has been used the participant should not be randomized until the test has been repeated. At a follow-up visit, if the participant refuses to repeat the Pad Test, leave the gram weight boxes (beside the missing used pad) blank on the original Pad Test form and enter 12 for the contamination code. Fax the form as usual.

Contamination Codes: Record the appropriate code for each used pad.

Code	Description
Record 01	if the pad is **not contaminated** with anything other than urine.
Record 02	if the pad is **soaked through** with urine.
Record 03	if the pad is contaminated with blood.
Record 04	if the pad is contaminated with stool.
Record 05	if the pad is contaminated with blood and stool.

Record 06 if the pad is soaked through with urine **and** contaminated with blood.
Record 07 if the pad is soaked through with urine **and** contaminated with stool.
Record 08 if the pad is soaked through with urine **and** contaminated with blood **and** stool.
Record 09 if you cannot identify the contaminant.

If Kits are returned with some pads missing:

OTHER CODES

Record 10 if the pad is missing and the participant reports that she **DID NOT USE** the pad during the 24-hour testing period.
Record 11 if the pad is returned and **NOT USED**.
Record 12 if the pad is missing and the participant reports that she **DID USE** the pad during the 24-hour testing period. This error will invalidate the test and the test should be repeated. Refer to the Operations Manual or call the CC for directions.

9. **Date Kit Returned:** Record the date the Pad Test Kit is returned. This should be the same date as the date the post-weight measurements are completed.

10.4.2.9 7-Day Voiding Diary (Number 2)

Follow the instructions in Section 9.3.3 for distribution and explanation of the 7-Day Voiding Diary. Note that the participant should complete the 24-Hour Pad test during days 4 – 7 of this Voiding Diary.

10.5 PRESENTING THE URODYNAMIC SUB-STUDY

A subgroup of 100 women (50 at each site) will have the opportunity to participate in the Urodynamic Sub-study (UDS). The UDS includes a standardized pelvic floor evaluation and urodynamic studies at baseline and at 6 months to elucidate the mechanism by which weight loss improves incontinence. This study is designed to (1) evaluate whether baseline urodynamic measures can identify women who are most

likely to experience improved continence after weight reduction and;
(2) examine the relationship of improvement in continence and changes in urodynamic measures.

All women who are eligible for PRIDE are eligible for the UDS but only the first 50 at each site who agree, will be randomized. The UDS visits are in addition to all regular visits for PRIDE.

Study personnel who discuss the UDS with participants should prepare by reading the UDS Protocol in Chapter 1 and the UDS procedures described in Chapter 11. The participant may be invited to watch the UDS informational slide presentation in addition to discussing the sub-study with PRIDE staff. A separate consent form and HIPPA authorization must be signed to participate in the sub-study. After 100 participants have had baseline UDS testing, the sub-study will no longer be presented as an option to women enrolling in PRIDE.

In order to minimize any bias of the main trial, participants in the sub-study will not be given their personal results until the end of the trial.

Once agreement to participate has been obtained, schedule the UDS visit by contacting the UDS study nurse according to local procedures. The UDS nurse will contact the participant, explain the procedures in more detail and arrange for the baseline UDS visit. Informed Consent for the Urodynamic Sub-Study will be reviewed and signed at the urogynecology site prior to the start of the UDS visit.

10.6 SCHEDULING THE RANDOMIZATION VISIT

The Randomization Visit should take place within 4 weeks of SV2.

Participants who are still eligible should leave the clinic with the following items:
- An appointment for the randomization visit
- 7-Day Voiding Diary #2
- 24-hour Pad Test Kit

10.7 SCREENING FORMS/Inclusion/Exclusion

At the end of each screening visit all the forms that have been collected or completed at that visit should be reviewed, and then faxed to the Coordinating Center data system. The Screening Visit checklist should be completed and faxed after Screening Visit 2 or at the time the participant is found to be ineligible.

The Inclusion/Exclusion form should be used during screening only to indicate that a participant has become ineligible for the study. For example, if the participant is found to be ineligible at SV1, then mark the one main reason and fax the Inclusion/Exclusion form at that time.

APPENDIX 10A
HOW TO COLLECT CLEAN URINE SAMPLE

How to collect a clean urine sample

6 easy steps for a clean sample

1. Wash and dry your hands thoroughly.

2. Remove the container cap and set it aside. Do not touch inner surfaces of container.

3. Wash your urogenital area with the towelette provided; wipe from front to back between the folds of skin.

4. Hold the lips of the vagina apart and begin urinating. Do not collect the first bit of urine you pass as this may be contaminated with bacteria from your skin or vaginal fluid. Let a small amount of urine pass into the toilet, then midway through, urinate into the container.

5. Replace the cap and tighten firmly.

6. Remember to wash your hands thoroughly after collecting the specimen.

APPENDIX 10B
Body Mass Index Table

BMI	Height(cm)																									
Weight kg.	150	154	154	156	158	160	162	164	166	168	170	172	174	176	178	180	182	184	186	188	190	192	194	196	198	200
60	27	26	25	24	24	23	23	22	22	21	21	20	20	19	19	18	18	17	17	17	16	16	16	15	15	15
62	28	27	26	26	25	24	24	23	22	22	21	21	20	20	19	19	19	18	18	17	17	16	16	16	16	15
64	28	28	27	26	26	25	24	24	23	22	22	22	21	21	20	19	19	19	18	18	17	17	17	16	16	16
66	29	29	28	27	26	26	25	24	24	23	23	22	22	21	21	20	20	19	19	18	18	17	17	17	17	16
68	30	30	29	28	27	26	26	25	25	24	23	23	22	22	21	21	20	20	19	19	19	18	18	17	17	17
70	31	30	30	29	28	27	27	26	25	25	24	24	23	23	22	21	21	20	20	20	19	18	18	18	18	17
72	32	31	30	30	29	28	27	27	26	25	25	24	24	23	23	22	22	21	20	20	20	19	19	18	18	18
74	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	21	21	20	20	20	19	19	19
76	34	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	21	21	20	20	20	19	19
78	35	34	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	21	21	21	20	20	19
80	36	35	34	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	22	21	21	20	20
82	36	36	35	34	33	32	31	30	30	29	28	27	27	26	26	25	25	24	23	23	22	22	22	21	21	20
84	37	37	35	35	34	33	32	31	30	30	29	28	28	27	26	26	25	25	24	23	23	22	22	22	21	21
86	38	37	36	35	34	34	33	32	31	30	30	29	28	28	27	26	26	25	25	24	23	23	23	22	22	21
88	39	38	37	36	35	34	33	32	31	30	30	29	28	28	27	26	26	25	25	24	23	23	23	22	22	21
90	40	39	38	37	36	35	34	33	33	32	31	30	30	29	28	28	27	26	26	25	25	24	24	23	23	22
92	41	40	39	38	37	36	35	34	33	33	32	31	30	30	29	28	28	27	26	26	25	25	24	24	23	23
94	42	41	40	39	38	37	36	35	34	33	32	32	31	30	30	29	28	28	27	26	26	25	25	24	24	23
96	43	42	41	40	38	38	37	36	35	34	33	32	32	31	30	30	29	28	28	27	26	26	25	25	24	24
98	44	43	41	40	39	38	37	36	35	35	34	33	32	32	31	30	30	29	28	28	27	26	26	25	25	24
100	44	43	42	41	40	39	38	37	36	35	35	34	33	32	32	31	30	29	29	28	28	27	26	26	25	25
102	45	44	43	42	41	40	39	38	37	36	35	34	34	33	32	31	31	30	29	29	28	28	27	26	26	25
104	46	45	44	43	42	41	40	39	38	37	36	35	34	34	33	32	31	31	30	29	29	28	28	27	26	26
106	47	46	45	44	42	41	41	39	38	38	37	36	35	34	33	33	32	31	31	30	29	29	28	28	27	26
108	48	47	46	44	43	42	41	40	39	38	37	36	36	35	34	33	33	32	31	31	30	29	29	28	28	27
110	49	48	46	45	44	43	42	41	40	39	38	37	36	35	35	34	33	32	32	31	31	30	29	29	28	28
110 +	49+	48+	46+	45	44	43	42	41	40	39	38	37	36	35	35	34	33	32	32	31	31	31	29	29	28	28

BMI	Height(in)																		
	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76
Weight (lbs)	4'10"	4'11"	5'0"	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'0"	6'1"	6'2"	6'3"	6'4'
100	21	20	20	19	18	18	17	17	16	16	15	15	14	14	14	13	13	13	12
105	22	21	21	20	19	19	18	18	17	16	16	16	15	15	14	14	14	13	13
110	23	22	22	21	20	20	19	18	18	17	17	16	16	15	15	15	14	14	13
115	24	23	23	22	21	20	20	19	19	18	18	17	17	16	16	15	15	14	14
120	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16	16	15	15	15
125	26	25	24	24	23	22	22	21	20	20	19	18	18	17	17	17	16	16	15
130	27	26	25	25	24	23	22	22	21	20	20	19	19	18	18	17	17	16	16
135	28	27	26	26	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16
140	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18	18	17
145	30	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18	18
150	31	30	29	28	27	27	26	25	24	24	23	22	22	21	20	20	19	19	18
155	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	20	20	19	19
160	34	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21	20	20
165	35	33	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21	20
170	36	34	33	32	31	30	29	28	27	27	26	25	24	24	23	22	22	21	21
175	37	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23	22	21
180	38	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23	22
185	39	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23
190	40	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23
195	41	39	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24
200	42	40	39	38	37	36	34	33	32	31	30	30	29	28	27	26	26	25	24
205	43	41	40	39	38	36	35	34	33	32	31	30	29	29	28	27	26	26	25
210	44	43	41	40	38	37	36	35	34	33	32	31	30	29	29	28	27	26	26
215	45	44	42	41	39	38	37	36	35	34	33	32	31	30	29	28	28	27	26
220	46	45	43	42	40	39	38	37	36	35	34	33	32	31	30	29	28	28	27
225	47	46	44	43	41	40	39	38	36	35	34	33	32	31	31	30	29	28	27
230	48	47	45	44	42	41	40	38	37	36	35	34	33	32	31	30	30	29	28
235	49	48	46	44	43	42	40	39	38	37	36	35	34	33	32	31	30	29	29
240	50	49	47	45	44	43	41	40	39	38	37	36	35	34	33	32	31	30	29
245	51	50	48	46	45	43	42	41	40	38	37	36	35	34	33	32	32	31	30
250	52	51	49	47	46	44	43	42	40	39	38	37	36	35	34	33	32	31	30
255	53	52	50	48	47	45	44	43	41	40	39	38	37	36	35	34	33	32	31
260	54	53	51	49	48	46	45	43	42	41	40	38	37	36	35	34	33	33	32
265	56	54	52	50	49	47	46	44	43	42	40	39	38	37	36	35	34	33	32
270	57	55	53	51	49	48	46	45	44	42	41	40	39	38	37	36	35	34	33
275	58	56	54	52	50	49	47	46	44	43	42	41	40	38	37	36	35	34	34
280	59	57	55	53	51	50	48	47	45	44	43	41	40	39	38	37	36	35	34
285	60	58	56	54	52	51	49	48	46	45	43	42	41	40	39	38	37	36	35
290	61	59	57	55	53	51	50	48	47	46	44	43	42	41	39	38	37	36	35
295	62	60	58	56	54	52	51	49	48	46	45	44	42	41	40	39	38	37	36
300	63	61	59	57	55	53	52	50	49	47	46	44	43	42	41	40	39	38	37

APPENDIX 10C
HEALTH HISTORY

Participant ID #	Acrostic	Date of Visit	Staff ID #
		Month / Day / Year	

HEALTH HISTORY
(Self-Administered)

Visit: ● Screening

16. Has a doctor ever told you that you had, or currently have, any of the following conditions or diseases?

a. A fistula or a hole in your bladder, rectum or near there?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

b. A birth defect leading to urine leakage?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

c. Urine leakage starting in childhood?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

d. Interstitial cystitis or very painful bladder?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

e. Problems with your spinal cord or back leading to urine leakage?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

Participant ID #	Acrostic	Date of Visit	Staff ID #
		Month / Day / Year	

HEALTH HISTORY
(Self-Administered)

Visit: ● Screening

16. (Continued)
Has a doctor ever told you that you had, or currently have, any of the following conditions or diseases?

f. Multiple sclerosis?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

g. Parkinson's disease?
- ○ Yes ⟶ **NOT ELIGIBLE**
- ○ No
- ○ Don't Know

17. Has a health care provider ever told you that you had, or currently have, hypertension?
- ○ Yes ⟶ If BP is ≥ 160/100 at RV, participant is **NOT ELIGIBLE**
- ○ No

18. Has a health care provider ever told you that you had, or currently have, high cholesterol?
- ○ Yes ⟶ Requires MD approval
- ○ No

19. Has a health care provider ever told you that you had, or currently have, coronary heart disease?
- ○ Yes
- ○ No

APPENDIX 10D
PAD TEST

Instructions for 24-hour Pad Test

- Complete the Pad Test in a 24 hour period between days 4 to 7 of the Voiding Diary days
- Prepare yourself the night before
- Start using a Study Pad the first thing in the morning when you wake up
- Avoid the use of vaginal creams, jellies, suppositories or douche treatments during the Pad Test
- Do not use tampons while completing the Pad Test, whether you are menstruating or not
- Avoid having intercourse while completing the Pad Test
- Complete the measures in your "typical" state (with or without a pessary)
- Write a "P" in the Toilet column of the Voiding Diary the hour you *start* the Pad Test
- On the next day when you complete the Pad test, write a "P" in the Toilet column in the hour you *end* the Pad Test
- If a Pad becomes '*soaked through'*, please check the box "Pad was soaked with urine" on the label of the zip-lock bag
- Please change the pad whenever you feel yourself leaking or damp
- Mark on the Pad Test Sticker the presence of blood or stool on individual pads
- Be sure to put used Pad back into the same zip-lock bag it came from
- Be sure to use Study Pads through the night of the Test to complete the entire 24-hours. The last Study Pad of the test will be the Pad you take off when you wake up the following morning.
- Do not use a Study Pad from the Pad Test Kit after the end of this 24-hour period. We ask that you return any of the pads you don't use to make the test accurate.
- Please remember to bring back all Pad Kit supplies (used and unused Pads) given to you when you return for your next visit.

If you have any questions, please call the Study Coordinator.

Telephone # _____

APPENDIX 10E
SCALE CALIBRATION LOG

Date	Actual weight 20gm wt	Actual weight 100gm wt.	Initials/Comments

APPENDIX 10F
WEIGHING PROCEDURE

The approved scale for weighing pads for the 24-hr Pad Test in PRIDE is Denver Instruments' XP-300 portable 300gram balance, accurate to .01gms. The scale has a stainless steel 5" x 7" weighing pan, calibrates automatically and can be operated by battery or with the AC adapter. It has a digital readout display and comes with a detailed Operations Manual that should be kept with the scale at all times.

A 200gm, Class 2 weight is required to calibrate the scale. The scale should be calibrated each day that it is in use.

The scale should be kept on a firm, level surface, away from vibration or magnetic materials. Avoid areas where there are fluctuations in room temperature or excessive hot or cold temperatures. Keep the scale covered, when not in use, to prevent dirt and dust from accumulating.

1. Turn the balance on and ensure that the units displayed are "grams". Use the down arrow key to scroll through the unit options if necessary.
2. Press the zero/tare button (-0-) to bring the scale to zero.
3. Calibrate the scale using the 200gm, Class 2 weight following the procedure described below.
4. Remove the 200 gm weight and bring the scale to zero again.
5. Fold the biohazard bag containing the pad in half and place it on the scale. Be sure that no part of the bag is protruding from the edges (fold in thirds if necessary).
6. Record the weight shown in the digital display panel on the Pad Test Form.
7. Continue weighing the biohazard bags with pads. The calibration procedure need not be repeated until the next time you use the scale.

Calibration Procedure

1. Tare or zero the balance with no weight on the pan.
2. Press and hold down the star key * for 3 seconds. The display will read "Unit".
3. Press the star key again once and the display will now show "CAL".
4. Press the down arrow ↓ key. The calibration weight of the balance in grams will be displayed.
5. Place the 200gm, Class 2 weight on the balance. After a few seconds the display will flash indicating that the value has been accepted.

CHAPTER 11

URODYNAMIC SUBSTUDY

11.0 URODYNAMIC SUBSTUDY

11.1 OVERVIEW PHYSICAL EXAMINATION & URODYNAMIC (UDS) TESTING

Equipment used for physical examination and urodynamic (UDS) testing in PRIDE will be the same equipment used in the Urinary Incontinence treatment Network (UITN) study. Procedures are similar also but the data recorded may be different in PRIDE and the instructions should be reviewed carefully before measurements begin.

A volunteer subgroup of 100 women in PRIDE will undergo a standardized pelvic floor evaluation and urodynamic studies at baseline and at 6 months to elucidate the mechanism by which weight loss improves incontinence. The UDS investigators will conduct exploratory analyses to evaluate whether baseline urodynamic measures such as intravesical pressures, Valsalva leak point pressures, and detrusor instability can identify women who are most likely to experience improved continence after weight reduction. They will also investigate the mechanism by which weight loss improves continence by examining the relationship of improvement in continence and changes in urodynamic measures.

The examination will consist of a physical examination (includes Pubococcygeus Contraction Assessment, Pelvic Organ Prolapse Quantification Exam (POP-Q) and the Q-Tip Test) and urodynamic testing (includes cough stress test, non-instrumented uroflow (NIF), post-void residual urine volume (PVR) and cystometric evaluation). All measures will be performed at baseline (before randomization) and at 6 months post randomization.

11.2 VISIT PROCEDURES

11.2.1 Physical Examination

11.2.1.1 Pubococcygeus Contraction Assessment

Instruments and Materials

- Stop watch accurate to a tenth of a second
- Glove
- Lubricating jelly

Procedure

This procedure is an adaptation of a test described by Brink, Sampselle, Wells, Diokno, and Gillis (*Nurs Res 1989 Jul-Aug;38(4):196-9*).

With the participant in the dorsal lithotomy (supine) position, explain that you will be testing her pelvic muscles using one or two fingers in the vagina. Also note that you will place your other hand alternately on her abdomen, hips, and thighs during the evaluation.

Gently insert the lubricated finger(s) (index or index and middle) 4-6 cm into the vagina with the palm facing down. Instruct the participant that you will be counting to three, and then ask her to "squeeze your pelvic muscles, the ones that you use to stop your urine stream, as strong as you can. I want you to hold the contraction for as long as possible or until I tell you to stop. As you do this, I want you to try to avoid contracting your tummy, bottom, or thigh muscles."

Any degree of flicker on the examiner's finger(s) is considered evidence of ability to contract the muscle. If the participant can accomplish this task without contracting other muscles, move on to the actual testing. If she cannot, continue coaching her with 1 to 3 more contractions until she contracts her pelvic floor muscles with minimal use of the accessory muscles. She may not be able to completely eliminate the use of the accessory muscles, but you want to minimize it as much as possible.

This test will assess three elements of the pubococcygeus muscle contraction: pressure, duration (using a stop watch that is accurate to the tenth of a second), and displacement. Duration is defined as the length at maximum contraction and stops when the strength of the contraction weakens. Maximum recorded value is 10 seconds even if participant can hold the contraction longer.

Data Points
The following data points will be recorded on every participant on the PUBOCOCCYGEUS CONTRACTION ASSESSMENT form:

- Pressure
- Duration – record to the nearest second
- Displacement of vertical plane

11.2.1.2 Pelvic Organ Prolapse Quantification Exam (POP-Q)

Overview
This procedure will be performed according to the guidelines

established by the International Continence Society (Am J Obstet Gynec (1996) 175:10-17) and will be standardized as demonstrated in a videotape produced by Duke University Medical Center ("Pelvic Organ Prolapse Quantification Exam").

Instruments and Materials

- Gynecologic chair
- Bivalve speculum
- Sims speculum
- Clear plastic ruler
- Graduated ring forceps

Procedure

Have the participant empty her bladder. The participant will then be positioned in a gynecologic chair in the supine position. The POP-Q will be performed in the supine position with prolapse maximized by having the participant strain or by valsalva.

Measure and record the maximum anterior-posterior length with maximum straining of the genital hiatus and perineal body. The genital hiatus is measured from the middle of the external urethral meatus to the posterior midline hymen with a clear plastic ruler. The location of the hymen may be distorted by a loose band of skin without underlying muscle or connective tissue. In such a case, the firm palpable tissue of the perineal body should be substituted as the posterior margin for this measurement. The perineal body is measured from the posterior margin of the genital hiatus to the mid-anal opening. Measurements of the genital hiatus and perineal body are expressed in centimeters.
Location of the Six Primary Measuring Points (Aa, Ba, C, D, Ap, Bp) in Centimeters. The anatomic position of the six defined points for measurement should be centimeters above or proximal to the hymen (negative number) or centimeters below or distal to the hymen (positive number) with the plane of the hymen being defined as zero (0). For example, a cervix that protruded 3 cm distal to the hymen would be + 3 cm.

a) **If all points are >0:** Measure the locations of the points distal to the hymen directly with a ruler, graduated rings forceps, or other measuring device while the participant is straining and the protrusion is

maximum. Then replace the vagina and measure the total vaginal length as noted below.

b) **If any points are ≤0 but some points are >0**: Measure and identify (if possible) the points >0 directly while the participant is straining and the protrusion is maximum. If point C is ≤0, insert a bivalve speculum to visualize the cervix or the cuff and withdraw it slowly while the participant is straining. Use the graduated ring forceps or other measuring device to measure the maximum descent of point C. Then use a Sims speculum to selectively retract the anterior and posterior vaginal walls to measure the maximum descent of any other points that are ≤0.

c) **If all points are ≤0:** Insert a bivalve speculum and measure the maximum descent of point C by having the participant maximally strain and withdrawing the speculum in conjunction with the descent of the cervix. Avoid tightening the bivalve speculum screws so as not to interfere with maximum descent. Then retract the posterior wall with a Sims speculum and measure the maximum descent of points Aa and Ba. Next, retract the anterior wall and measure the maximum descent of points Ap and Bp.

Location of Point D. Point D is omitted as a point for measurement in the absence of the cervix. When it is located at ≤0 cm, its location can be measured either during the bivalve speculum examination as described for the location of the cervix (point C) above or by palpation relative to the position of the cervix during the digital examination for the determination of total vaginal length. For example, if the cervix is visualized to descend –2 cm and the posterior fornix is palpated to be 2 cm proximal to the cervix, the position of point D would be –4 cm. When Point D is >0, its location is measured directly. In cases of total uterine prolapse with vaginal eversion with the cervix as the most distal (dependent) point, Point D will be assigned a value equal to the value for Points Ba, Bp, and C.

Determination of Total Vaginal Length. Point C or D is digitally reduced with one or two fingers to its full extent without putting the wall on excessive tension. Eccentric elongation of a prolapsed anterior or posterior vaginal wall should not be included in the measurement of total vaginal length. In such a case, the total vaginal length is not the

maximum depth of the vagina with the elongated vaginal wall maximally reduced, but rather the depth of the vagina at the cuff with Point C or D reduced to its full normal extent. With the prolapse maximally reduced, insert the measuring device and measure from the vaginal cuff to the hymenal ring.

Data Points
The following data points will be recorded on every participant on the PELVIC ORGAN PROLAPSE QUANTIFICATION POP-Q form:

- Points Aa, Ba, C, D, Ap, Bp, GH, PB, TVL. Round to the nearest 0.5 cm
- Stage of prolapse

11.2.1.3 Q-Tip Test

Overview
The Q-Tip test will be used to quantify bladder neck hypermobility. The testing procedure will be standardized as described below.

Instruments and Materials
- Robinson Pocket goniometer (7.25", 180º with a 5º increment)
- Sterile cotton or dacron swab
- Lubricating anesthetic jelly

Procedure
Insert a sterile, lubricated cotton or dacron swab (Q-Tip) into the urethra until it lies just within the urethrovesical junction. Using a Robinson Pocket goniometer (7.25", 180º with a 5º increment), measure the angle circumscribed by the distal end of the swab relative to the horizontal at rest. Ask the participant to perform a maximum Valsalva effort while lying flat in the dorsal lithotomy (supine) position. Using the goniometer, measure the angle of the distal end of the swab at maximum straining relative to the horizontal. A positive (+) angle is above the horizontal plane and a negative (-) angle is below the horizontal plane. Bladder neck hypermobility is defined as a resting angle >30 degrees OR a maximum straining angle >30 degrees.

Data Points
The following data points will be recorded for every participant on the

URETHRAL HYPERMOBILITY (Q-TIP TEST) form:

- Angle at rest record + or – and degrees of the angle
- Angle at maximum straining:record + or – and degrees of the angle

11.2.1.4 Cough Stress Test

A screening test for urinary tract infection will be done prior to the stress test. When there is suspicion for infection, a urine culture will be done. Stress tests that are positive in the face of positive urine cultures will be repeated when the infection is resolved.

Stress incontinence is considered present when the participant demonstrates transurethral urine leakage with or immediately after increased intra-abdominal pressure (with Valsalva effort or coughing). The stress test will be performed as follows:

- The participant voids.
- If the participant has prolapse, this is not reduced.
- Using a 14Fr catheter, the bladder is emptied.
- Beginning from an empty bladder, the bladder is retrograde gravity filled to 300 ml or maximum capacity with sterile water, whichever is less. The catheter is removed.
- In the supine position, the participant is asked to Valsalva and cough. If leaking is noted, no further testing need be performed. If no leaking is noted and the participant has grade III or IV anterior prolapse, the prolapse will be reduced with rectal swabs and the Valsalva and cough will be repeated. If no leaking is noted, the participant stands and is asked to Valsalva and cough. If no leaking is noted and the participant has grade III or IV anterior prolapse, the prolapse will again be reduced and the Valsalva and cough will be repeated. Any positive stress test is noted. Before recording a negative stress test, the standing position and maximal cough must be performed.
- It is not necessary to quantify the amount of urine lost with leakage.

Data Points for the Cough Stress Test
The following data points for the NIF will be recorded on every patient on the STRESS TEST data form:

- Did the participant demonstrate stress urinary incontinence – have a urine loss - at a bladder volume ≤300 ml during the Stress Test?: yes or no. If "yes", complete questions 1a. and 1b. If yes:
  - Was suspicion of a detrusor contraction?
  - Did the stress incontinence occur with valsalva in the supine position?
  - Did the stress incontinence occur with cough in the supine position?
  - Did stress incontinence occur with valsalva in the standing position?
  - Did the stress incontinence occur with cough in the standing position?
  - Was it necessary to reduce a Stage III or IV anterior prolapse to complete this Stress Test?

11.2.1.5 Non-Instrumented Uroflowmetry (NIF)

To be performed after 300 cc cough stress test.

Instruments and Materials
- Uroflowmeter
- Urodynamic recorder
- Catheter

Any of the electronically derived methods of calculating the uroflowmetry values are acceptable. The uroflowmeter should be calibrated every three months to be certain that they match calibration standards as described in your equipment specifications manual. Calibrations should be completed when measures fall outside of the standards. Sites should keep a log of the calibration checks completed including date performed and signature of the person completing the calibration check **(Appendix 11A)**.

The scale should be set to zero prior to the start of each participant's study.

Procedure
After the 300 cc provocative stress test, the participant will be positioned on the Uroflow chair . The participant will void into the uroflowmetry

machine while in the upright sitting position.

A time-flow curve will be recorded using a standard urodynamic recorder. Flow pattern should be classified as either normal or abnormal. To classify the flow pattern as normal, the signal must be **continuous, smooth and arc shaped with high amplitude. Any signal that does not meet these criteria should be classified as abnormal. (SEE APPENDIX 11C - EXAMPLES OF FLOW CURVES)**

Abnormal flow patterns fall into several subcategories, including:

- **Interrupted**: signal returns to baseline due to intermittent sphincter activity;
- **High amplitude**: signal has more than one peak or a fluctuating peak, indicating a fluctuating flow pattern; or
- **Low amplitude:** signal is either

    - continuous and flat, indicating a constrictive flow pattern, or
    - signal has an initial peak with a down slope indicating a compressive flow pattern.

Following the NIF, a post-void residual urine volume (PVR) will be obtained by inserting a small catheter into the bladder and measuring the PVR volume. If this PVR is < 150, record "999" for the PVR #2 value on the data form. If the PVR volume is > 150cc, repeat the PVR after the CMG and record as PVR # 2 on data form. If the repeat PVR is not done, leave the data field blank.

Data Points for the NIF

The following data points for the NIF will be recorded on every patient on the NON-INSTRUMENTED UROFLOWMETRY (NIF) form:

- Maximum flow rate (ml/sec)
- Mean flow rate (ml/sec)
- Flow pattern (normal or abnormal)
- Time to maximum flow (sec)
- Voided volume (ml)
- PVR (ml)

11.2.2 UDS Measurements

11.2.2.1 Filling Cystometrogram (CMG)

Instruments and Materials

- A multi-channel urodynamics recorder
- External pressure transducers
- Fluid-filled column type urodynamics tubing
- ≤ 8 French dual lumen transurethral catheter
- A standard manufactured rectal balloon catheter
- Room temperature sterile water
- Robinson Pocket goniometer (7.25", 180º with a 5º increment) or angle of recline measure on urodynamic chair

A fluid column-type urodynamics catheter is required by protocol, no other types of electronic or light sensing catheters are allowed. The urodynamics catheter used for the CMG must be dual lumen, ≤8 French.

Flow and pressure transducer equipment should be checked every three months to be certain that they match calibration standards as described in your equipment specifications manual. Calibrations should be completed when measures fall outside of the standards. Sites should keep a log of the calibration checks completed including date performed and signature of the person completing the calibration check **(Appendix 11A)**

Procedure

To maintain consistency across centers, the CMG should be obtained while the participant is in a sitting position in a 45 degree reclined position. Using a Robinson Pocket goniometer, measure the angle of the urodynamic chair relative to the horizontal and confirm the 45 degree angle.

The fluid-filled column-type tubing will be connected to the intravesically placed catheter and the bladder filled with room temperature sterile water at a rate of 50 ml/min. A rectal catheter will be used to measure continuous intra-abdominal pressure. One of the standard manufactured rectal balloon catheters should be used.

Intravesical pressure (Pves), intra-abdominal pressure (Pabd), and

subtracted detrusor pressure (Pdet) should be continuously recorded on a multichannel urodynamics recorder throughout the conduct of the CMG. Flow rate and volume should also be continuously recorded. Prior to the start of filling, the external transducers must be positioned at the upper level of the symphysis pubis and Pves and Pabd should be simultaneously zeroed to atmospheric pressure.

Insert the transurethral and rectal balloon catheters. Instruct the participant to cough to assess proper placement of the catheters and to document the dynamic response of the pressure channels. The Pves and Pabd signals (tracings) should demonstrate good tracking and the Pdet should be between 0 and 5 cm/H_2O at this time. If not, the catheters should be flushed, their position should be evaluated and other troubleshooting measures taken. A negative Pdet reading should also prompt immediate troubleshooting. Excessive rectal balloon filling may cause abnormally high Pabd readings and the balloon volume may need to be adjusted. Filling should commence when Pabd and Pves pressure signals document the dynamic response of the pressure channels and the Pdet is between 0 and 5 cm/H_2O.

Document Pves and Pabd at baseline with an annotation line on the signals (tracing).

At a bladder volume of 100 ml, instruct the participant to cough and reassess proper placement and function of the catheters and transducers (**annotate this cough on the signal**). Look for the dynamic response of the pressure channels. If pressures channels do not track at this time, repeat troubleshooting measures.

Bladder Sensation Parameters: Three bladder sensation parameters should be measured during filling cystometry. The participant should be instructed to state when she has the sensation of 1) first desire to void, 2) strong desire to void, and 3) sensation of maximum cystometric capacity, using the following standardized definitions/descriptions.

First Desire to Void: When filling commences, instruct the participant that you need to know when she has a *first desire to void*. This is defined as "the feeling, during filling cystometry that would lead the participant to pass urine at the next convenient moment, but voiding can be delayed if necessary". Tell the participant:

"*If you are watching TV, tell me when you would go to the bathroom at the next commercial*."

Strong Desire to Void: After this milestone is reached, instruct the participant that you need to know when she has a s*trong desire to void.* This is defined as "a persistent desire to void without the fear of leakage." Tell the participant:

"*Tell me when you can't wait for the next commercial."*

Maximum Cystometric Capacity: After this milestone is reached, proceed to *maximum cystometric capacity (MCC)* which is defined as "the volume at which the participant feels she can no longer delay micturition." Tell the participant:

"*I need to know how much your bladder can hold. Let me know when you can't take any more in your bladder."*

11.2.2.2 Obtaining Intravesical Valsavla Leakpoint Pressures (VLPP)

For study purposes, we will measure and record the absolute intravesical pressure (raw Pves) during the Valsalva maneuver that produced leakage. For further reference in this Procedure Manual, we will call this measurement from the zero baseline, the Valsalva Leak Point Pressure (VLPP). [Other calculated VLPP measurements from different baselines (e.g. baseline Pves) will be done only by the CC during analysis.] To avoid confusion, Investigators are asked **not to** record any calculated VLPPs on the Data Form. For this trial, a mean of three intravesically measured VLPP values will be obtained to ensure test precision and to evaluate reproducibility. In the event that leakage cannot be reproduced with up to five Valsalva maneuvers, despite careful coaching, two VLPP values will be accepted.

To accurately determine VLPP, Testers should observe for urine leakage coincidental with Valsalva maneuvers. Testers may employ several techniques to observe the urethra while simultaneously annotating the signals including:

1) Two-person exam: An assistant may annotate the signals on the directive of the primary Tester as s/he completes the observation.

2) Use of a remote keypad device: A remote keypad device may be used to allow the Tester to annotate the signals from a location distant from the computer keyboard.
3) Adequate participant coaching: If the participant is instructed to relax the instant she hears the Tester says the word, "Leak," the VLPP can be annotated at the maximum point of the spike of the Valsalva maneuver on the signals.

To coach the participant to perform Valsalva maneuvers correctly, instruct her to bear down slowly, incrementally increasing her effort until leakage occurs or the maximum amount of straining is reached. When leakage occurs, annotate the first VLPP. Have the participant repeat the Valsalva maneuver two more times to obtain 3 VLPP measures at the same volume. All 3 VLPP values should be annotated on the signals. If the participant has one leakage with Valsalva during 3 Valsalva maneuvers, repeat for a total of five Valsalva maneuvers. If the participant leaks with only one of five Valsalva maneuvers, the leakage is considered a false positive finding and not recorded. Proceed to the next volume for testing and repeat the protocol as described. For each Valsalva maneuver after the initial leakage, the participant needs to Valsalva to reach either leakage or the Pves observed during the effort when the leakage occurred. (Leakage must occur at least twice with Valsalva maneuvers at the same volume to be recorded as the VLPP.)

Follow the appropriate procedures for participants with or without anterior prolapse Stage III or IV as described below.

Procedures for participant without anterior prolapse Stage III or IV (anterior prolapse ≤ Stage II) (See UDS Flow Diagram A attached)

If the participant **does not have** a large anterior prolapse (i.e. Stage III or IV), only unreduced VLPP measures will be obtained.

Reminder: Annotate VLPP and loss with maximal cough on the signal. Check each annotation to assure that they are at the correct position and provide accurate assessment of the Pves at time of leakage.

Stop the infusion at **200 ml** and perform Valsalva maneuvers as described above. If leakage is observed at the 200 ml volume, repeat Valsalva maneuvers two more times to obtain 3 VLPPs at the 200 ml

volume, record/annotate the VLPP measures on the signals. Instruct the participant to cough maximally and observe for urine leakage. Cough until leakage occurs or 3 maximal coughs are done. Record/annotate the loss with cough on the signals and record the loss with cough and volume at loss on the CMG Data Form. Resume infusion to determine the MCC.

<u>If leakage is not observed with Valsalva at 200 ml volume</u>, resume infusion and repeat both Valsalva and cough maneuvers at each 100 ml increment until leakage is observed or MCC is reached. When leakage is observed, determine the VLPP values per the procedures described above, then resume infusion to determine MCC. When leakage is observed with cough, record volume on data form and no further cough testing is needed.

If the participant reaches MCC without demonstrating leakage, instruct her to cough maximally and observe for urine leakage. Record the presence or absence of urodynamic stress incontinence at MCC. If leakage is not observed, remove the transurethral catheter and instruct her to cough maximally while you observe for urine leakage. If leakage is still not observed, instruct the participant to stand, repeat a maximal cough, and observe for urine leakage. Record no loss or loss (and volume) on data form.

Regardless of the volume at which the participant leaks, the bladder volume at first desire to void, strong desire to void, and MCC should be determined and annotated on the signals. The **Pves** and **Pabd at MCC** should also be annotated on the signals.

If micturition of > 100ml occurs or or >100ml of fluid is otherwise lost during the performance of the CMG, the test should be re-started after completely emptying the bladder to ensure accurate bladder volumes.

All critical data points should be annotated on the signals.

If the PVR following NIF is > 150 ml, have participant void and repeat PVR. Record on the NIF Data Form as Measured PVR #2. If the repeat PVR is not done, leave the data field blank.

Procedures for participant **<u>with</u> anterior prolapse Stage III or IV (See**

Flow Diagram B attached)

If the patient has a large anterior prolapse (i.e. Stage III or IV), VLPPs will be measured with and without reduction of the prolapse at 200ml. **After 200ml, the prolapse will be reduced for measurement of the VLPPs and maximal cough.** Prolapse reduction should be performed with a rectal swab.

Reminder: Annotate VLPP and loss with maximal cough on the signal. Check each annotation to assure that they are at the correct position and provide accurate assessment of the Pves at time of leakage.

Prior to reduction of the prolpase, perform Valsalva maneuvers as described above at the 200ml volume.

- **If the "unreduced" participant leaks at 200ml,** repeat Valsalva maneuvers two more times to obtain 3 VLPPs. Annotate the "unreduced" VLPPs on th esignal, then reduce the prolapse, and attempt "reduced" VLPPs at 200ml. If the participant leaks with reduction, annotate the "reduced" VLPPs. With prolapse reduced, instruct the participant to cough maximally and observe for urine leakage. Cough until leakage occurs or 3 maximal coughs are done. Then maintain the prolapse reduction and resume infusion to determine the participant's MCC. Repeat the maximal cough test at 100 ml increments until the participant leaks with cough or reached MCC. If the participant leaks with maximal cough before reaching MCC, continue bladder filling to MCC. Record/annotate the loss with cough on the signals and record the loss with cough and volume at loss on the CMG Data Form.
- **If the "unreduced" participant doesn't leak at 200 ml,** reduce the prolapse, and attempt "reduced" VLPPs. If the participant leaks with reduction, annotate the "reduced" VLPPs on the signal. With prolapse reduced, instruct the participant to cough maximally and observe for urine leakage. Cough until leakage occurs or 3 maximal coughs are done. Then maintain the prolapse reduction and resume infusion to determine the participant's MCC. Repeat the maximal cough test at 100 ml

increments until the participant leaks with cough or reached MCC. If the participant leaks with maximal cough before reaching MCC, continue bladder filling to MCC. Record/annotate the loss with cough on the signals and record the loss with cough and volume at loss on the CMG Data Form.

- **If "reduced" VLPPs cannot be obtained at 200ml,** maintain the reduction and repeat Valsalva and maximal cough maneuvers at successive 100ml increments until leakage occurs or MCC is reached. Both the Valsalva and maximal cough maneuvers should be done at 100 ml increments until leakage occurs OR MCC is reached. If the participant doesn't leak at MCC with Valsalva maneuvers, instruct her to cough maximally, described above, and observe for urine leakage. If leakage is not observed, remove the transurethral catheter and instruct her to cough maximally while you observe for urine leakage. If leakage is still not observed, remove the prolapse reduction, instruct the participant to stand, repeat a maximal cough, and observe for urine leakage. If leakage is still not observed, reduce the prolapse and repeat the maximal cough testing. Record no loss or loss (and volume) on data form. Record the presence or absence of urodynamic stress incontinence at MCC.

Regardless of the volume at which the participant leaks, the bladder volume at first desire to void, strong desire to void, and MCC should be determined and annotated on the signals. The **Pves and Pabd at MCC** should also be annotated.

If micturition of > 100 ml occurs or >100 ml is otherwise lost during the performance of CMG, the test should be re-started after completely emptying the bladder to ensure accurate bladder volumes.

All critical data points should be annotated on the signals.

If the PVR following NIF is > 150 ml, have participant void and repeat PVR. Record on the NIF Data Form as Measured PVR #2. If the repeat PVR is not done, leave the data field blank.

CMG Data Points

For every participant: The following data points for the CMG will be

obtained for **every** participant and recorded on the CYSTOMETOGRAM (CMG) AND LEAK POINT PRESSURE (LPP) form.

- Catheter diameter
- Pves at baseline (cm/H_2O)
- Pabd at baseline (cm/H_2O)
- Bladder volume at first desire to void (ml)
- Bladder volume at strong desire to void (ml)
- Prolapse status (Stage III or IV anterior prolapse – yes or no)
- Leakage with valsalva (yes or no) – to code this as "yes", leakage must occur with valsalva at least twice at the same volume)
- Bladder volume at leakage with valsalva (ml)
- Pves at leakage (VLLP) [two measures are required]
- Bladder volume at MCC (ml)
- Leakage with cough and bladder volume at leakage
- Pves at MCC (cm/H_2O)
- Pabd at MCC (cm/H_2O)
- Detrusor overactivity (yes or no) Volume at each occurrence (ml)
    - Detrusor overactivity incontinence (yes or no)

For participants with Stage III or IV anterior prolapse: The VLLP tests will be performed without then with reduction of the prolapse. The following additional data points will be obtained and recorded for participant with a Stage III or IV anterior prolapse:

- Method used to reduce the prolapse (rectal swab, ring forcep, speculum, other)
- Leakage with valsalva (yes or no) following prolapse reduction – to code this as "yes", leakage must occur with valsalva at least twice at the same volume)
- Bladder volume at leakage with valsalva (ml) after prolapse-reduction
- Prolapse reduced Pves at leakage (VLLP) [two measures are required]

Calculated data points: The following data points for the CMG will be **calculated** by the UCSF Coordinating Center on every participant prior to analyses:

- Bladder compliance *[MCC/ (Pves at MCC - Pves at baseline)]*

- Mean of VLPP values obtained for unreduced and reduced measurements
  [mean Pves = (Pves 1 + Pves 2 + Pves 3) / 3] or [mean Pves = (Pves 1 + Pves 2) / 2]
- VLPPs from different baselines with and without reduction *(mean Pves - Pves at baseline)*

11.3 QUALITY CONTROL

Several testing standards have been established by the Urinary Incontinence Treatment Network (UITN) UDS Working Group in an effort to minimize variability of UDS completion and interpretation across Testers / Observers. These UITN standards have been adopted for the PRIDE. Standards documented herein are in keeping with several of the recommendations of the ICS Standardization Committee of Good Urodynamic Practice recently published by Schafer and others (Schafer et. al. 2002).

All technicians performing the physical and UDS examinations on PRIDE participants must be certified according to UITN and/or PRIDE procedures and certification must be renewed annually.

11.3.1 Standards for Signals (AKA: tracings, graphs, recorder output)

An original printout of the UDS signals (tracings) should be retained in the participant's research record and another printout (preferably another original) should be mailed to the central repository at the CC along with all other required source documentation. UDS signals should be mailed to the coordinating center following data management and data transmission procedures described elsewhere.

A) **Graph scaling:** In keeping with recommendation of the ICS standardisation committee of good urodynamic practice (schafer, et. Al. 2002), the scaling of the signals will be standardized across centers and kept unchanged as much as possible. Urodynamic quality control is dependent on the tester's ability to recognize patterns, and the recognition of patterns will be greatly improved by standard scaling of the signals:
   I. The graphing scaling for the <u>non-instrumented uroflow</u> signals will be standardized as follows:
      One millimeter will equal 1 s on the x-axis for both Flow and Volume; and on the y-axis, 1mm will equal 1ml/s for

Flow and 1 mm will equal 10 ml for Volume.

II. Graphing for the CMG signals should follow these conventions: During recording and for analyses, a minimum scaling for pressures will be set at 50cm H_2O per cm; 25ml/s per cm for Flow; and 1min per 3cm for the time axis.

III. For all study signals, the scales for the x-axis and the y-axis must be clearly indicated.

B) **Labeling:** The signals of each respective study must be clearly labeled; i.e. non-instrumented uroflowmetry (NIF) vs. CMG, to simplify a central review. The CC will provide a labeling system for sites.

C) **Annotation:** The signals should be annotated in accordance with the required PRIDE data points. A list of the required annotations is included here as Attachment 11B.

11.3.2 Source Documentation

For each completed UDS, the clinical site must send the source documentation of the Urodynamic recorder signals (aka tracings, graphs, output) from each of the required urodynamic studies to the central repository at the UCSF Coordinating Center (CC).

11.4 DATA FORMS

11.4.1 Reviewing the Data

A PRIDE Physician Investigator must verify, validate and confirm that the UDS was completed in accordance with sound clinical practice and in compliance with the PRIDE UDS protocol. S/he must also provide a clinical interpretation of the UDS and must review or complete the PRIDE Data Forms.

To minimize invalid and missing data, a PRIDE Physician Investigator or certified UDS examiner must review the UDS signals prior to removal of the catheters. If valid UDS data points cannot be abstracted from the signals, studies should be repeated whenever clinically feasible.

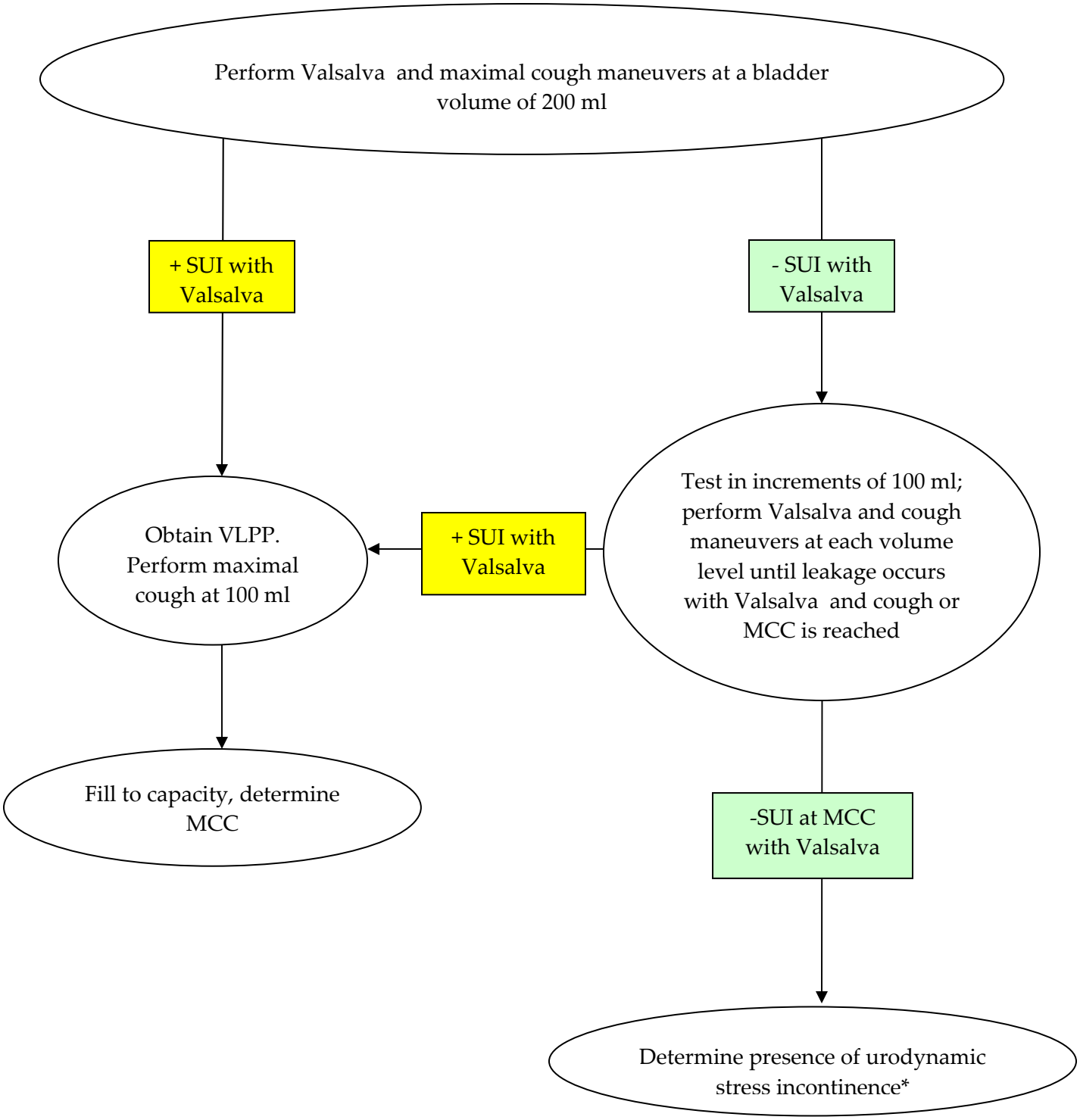
UDS data points that are artifactual, not interpretable, or deemed invalid by the PRIDE Physician Investigator should not be recorded on a PRIDE Data Form. If studies cannot be repeated, these data fields should be filled with the special missing values code, negative 6 (-6) to indicate the data are deemed invalid . In such instances, a brief explanation regarding the reason for the

missing data should be written in the special text field provided on the Data Form.

11.4.2 Completing the Data Forms

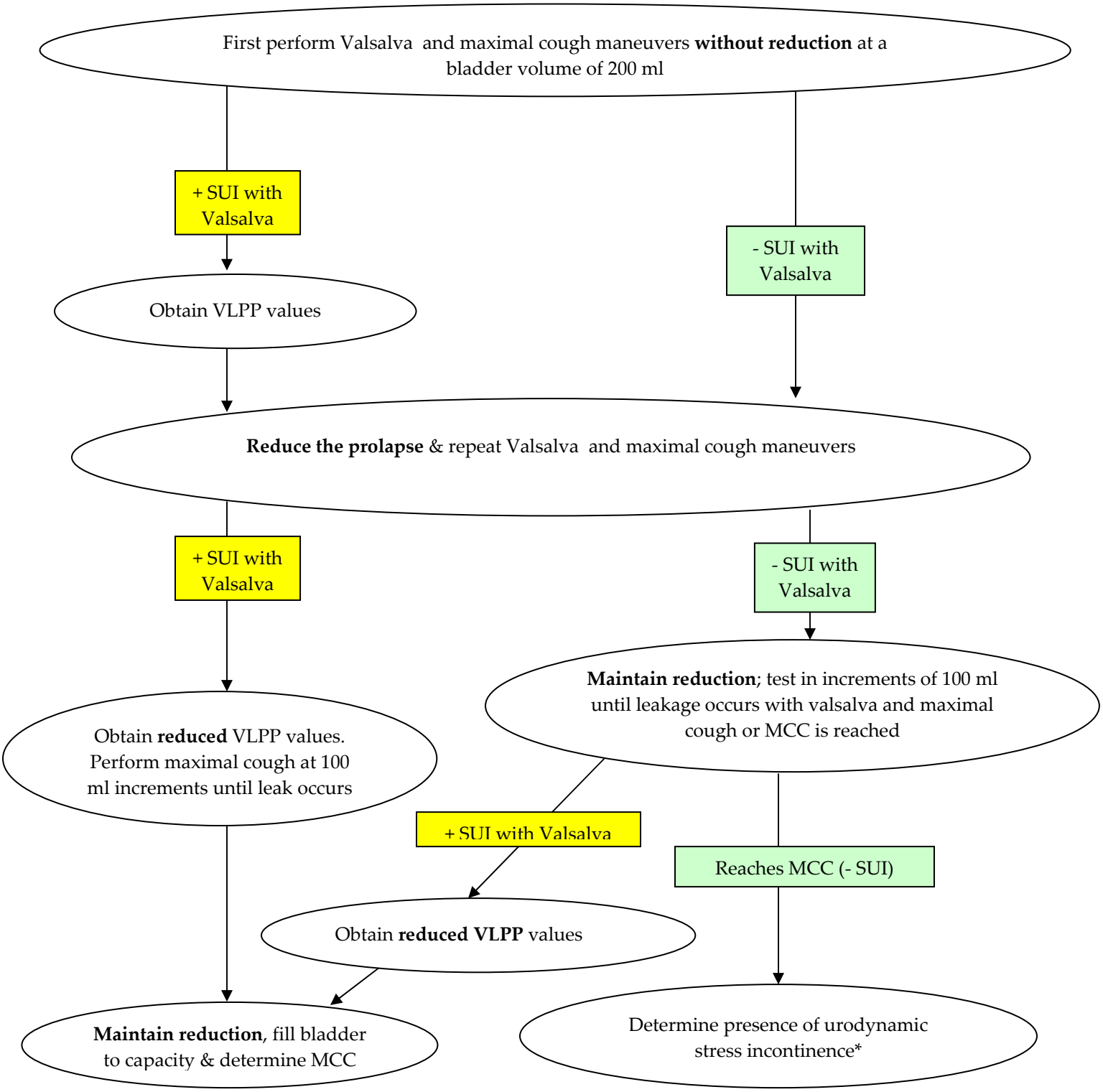
After the visit, the UDS Study Nurse should review the data forms carefully, checking for missing or misplaced values. Then the data forms should be faxed to the UCSF data system. Queries that are generated on UDS forms will be reviewed on-line by the UDS staff for the appropriate corrections.

UDS Flow Diagram A: <u>without</u> Anterior Prolapse Stage III or IV



*Test until leakage occurs or no leakage on standing test. Order of testing: valsalva maneuvers, maximal cough, remove catheter and do maximal cough, standing position with maximal cough.

UDS Flow Diagram B: <u>with</u> Anterior Prolapse Stage III or IV



* Test until leakage occurs or no leakage on standing test. Order of testing: valsalva maneuvers, maximal cough, remove catheter and do maximal cough, standing position with maximal cough.

Appendix 11A

CALIBRATION LOG

1. Calibrate the urodynamic equipment every 3 months in accordance with calibration standards described in your equipment specifications manual.
2. Record the measurement under "Trial 1".
3. If measures fall outside of the standards, calibrate your equipment and repeat the calibration check.
4. Record second measurement (if necessary) under "Trial 2".

Date	Trial 1	Trial 2	Staff ID#

Appendix 11B

STANDARD ANNOTATIONS FOR UDS

Non-Instrumented Uroflowmetry (NIF):

- Uroflow Voiding Start
- Max. Flow
- Uroflow Voiding Stop
- Artifact

Cystometrogram (CMG):

- CMG Baseline (Pves & Pabd at baseline)
- CMG Start (start of infusion)
- Cough at 100 ml
- First Desire
- Strong Desire
- Prolapse Reduced (if applicable)
- Valsalva No Leak
- Valsalva Leak (VLPP)
- MCC (Pves, Pabd, & volume)
- Cough at MCC-Leak
- Cough at MCC-No Leak
- Detrusor Overactivity-Leak
- Detrusor Overactivity-No Leak
- CMG Stop (stop of infusion)
- Reduction removed

Misc. Terms:

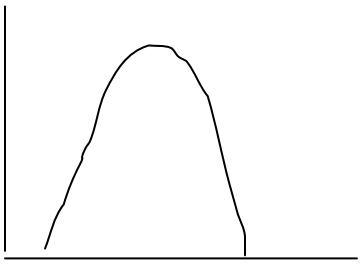
- Unable to Void
- Pves Cath. Fell Out
- Pabd Cath. Fell Out
- Bladder Refilled
- Void
- Artifact
- Laughing
- Cough
- Pves Cath. Flushed
- Pabd Cath. Flushed
- Pves Cath. Adjusted
- Pabd Cath. Adjusted

Appendix 11C

CLASSIFICATION & EXAMPLES OF FLOW PATTERNS IN THE NON-INVASIVE UROFLOW STUDY

Normal (according to Schafer's description):

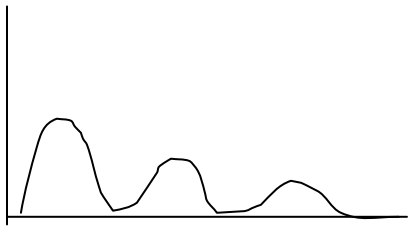
- "smooth, arc-shaped, with high amplitude"
- continuous



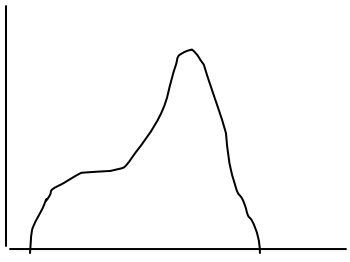
Abnormal:

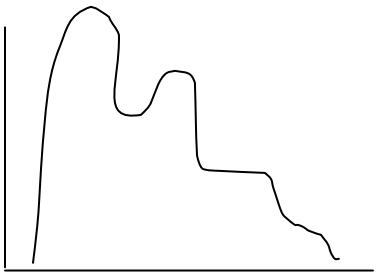
- Interrupted, i.e. signal returns to baseline due to intermittent sphincter activity
- High amplitude: More than one peak or a fluctuating peak
- Low amplitude:
  - Flat: continuous (constrictive)
  - Initial peak, with down slope (compressive)

Interupted

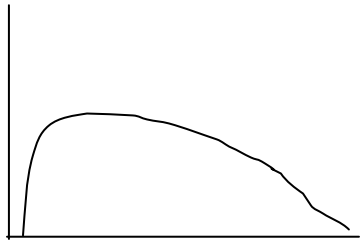


High amplitude

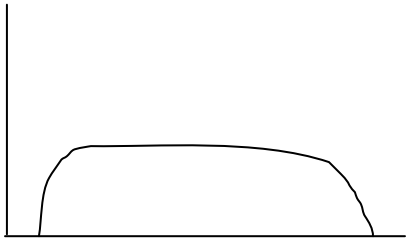




Low amplitude



Compressive



Constrictive

CHAPTER 12

RANDOMIZATION VISIT AND PROCEDURES

12.0 RANDOMIZATION VISIT

12.1 OVERVIEW

Randomization occurs after all eligibility requirements have been met and after all baseline measures have been completed.

Women will be randomly allocated in a 2-to-1 ratio to either the weight reduction program or control. The randomization will be stratified both by center and whether or not the participant volunteers for the urodynamic assessment.

Two sets of opaque, sealed, randomization envelopes will be provided to each site; white envelopes for women enrolling in the main study only and manila envelopes for women who agree to have the urodynamic assessment.

On the outside, the envelopes will be numbered consecutively with the randomization sequence number; on the inside the envelopes will contain study group assignment. The intervention group will also be assigned to either group A or group B to facilitate the re-randomization at 6 months. Opened and unopened envelopes will be stored at the site in a locked cabinet in the correct numbered sequences.

12.2 PREPARATION FOR THE VISIT

This is the last occasion prior to randomization to confirm the participant's eligibility for PRIDE. The participant can be randomized at any point during the visit as long as all inclusion/exclusion criteria have been met.

Forms/Procedures Needed for Randomization Visit

Review 2nd 7-Day Voiding Diary
Weight and Abdominal Circumference
UI Symptoms
Collect/Weigh 24-Hour Pads
Randomization/Inclusion/Exclusion Checklist
Randomization Envelopes
Staying Dry Handbook

Please have a calculator available.

12.3 RANDOMIZATION VISIT PROCEDURES

12.3.1 Review of 2nd 7-Day Voiding Diary

Collect the 2nd 7-Day Voiding Diary from the participant and review her daily entries following the procedures described in Chapter 10.3.2.2. Fill out the Voiding Diary Data Entry Form according to Chapter 10.3.2.3, marking the "RV" bubble. Check to make sure the 24-hour Pad Test was completed during the week that voiding episodes were recorded in the diary. If the Pad Test was not completed during the week that incontinence episodes were recorded the test is invalid and should be repeated. In this case it will be necessary to repeat the 7-day Voiding Diary also. Note that this does not affect the participant's eligibility.

The participant has already met the eligibility criterion for voiding episodes based on her screening visit diary. If there are less than 10 episodes of incontinence per week recorded on the randomization visit diary, the participant is still eligible for the study. However, please discuss the diary with the participant to be sure she hasn't forgotten to record episodes of incontinence.

If the diary is not returned or has not been completed for at least 5 of the 7 days, it should be repeated, along with the Pad Test. If the participant does not return an adequately completed diary she is not eligible to be randomized and you should mark the Inclusion criterion I as "No".

12.3.2 Collection/Weighing of Pad Test

When the participant returns the completed Voiding Diary and the Pad Test Kit (including all used and unused pads) the study nurse weighs each of the pads in the Kit and completes the remaining sections of the Pad Test data form.

Use gloves and do not remove the pad or the staple from the biohazard bag prior to the weighing. Dispose of used pads in a biohazard container. Please weigh the pads within 24 hours of receipt so as not to lose any of the urine due to evaporation.

Follow the instructions in Chapter 10.4.2.8 for weighing the pads. Post-test

weights should be performed by a certified PRIDE staff-member, preferably the same person who performed the pre-test weights.

Pad Test Form

Check the banner information, the visit bubble and the date of the pre-weights on the Pad Test Form before entering the post-weights. Parts 1 – 4 of the Form should be filled in already.

Complete the Pad Test Form as follows:

5. **Date post-weights are recorded:** Record the date when post-weight measurements are documented on the Data Form.

6. **Post-weight:** Weigh each used pad following procedures described in Appendix 10 F. Record the pad weight in grams to the nearest .01-gram weight.

Contamination Code: Review the self-report label on each biohazard bag and confirm with the participant to determine and record a contamination code. Do not weigh unused pads; leave the gram weight boxes blank.

- If the pad is missing but the participant reports that she did not use it , leave the gram weight boxes blank and enter "10" as the contamination code.
- If the pad was returned but not used, enter "11" as the contamination code for that pad.
- If the pad was returned, used but there appears to be nothing on it (not even urine) use the code "01".

If the pad is missing and the participant reports that she *did* use it, the test is invalid and should be repeated. It is very important that all used pads be weighed. In the case of a missing *used* pad, do not complete or fax the form; write "Invalid Test" across the form and file it in the participant's binder. Prepare another Pad Test Kit for the participant and print out a new Pad Test form. When a pad is missing but has been used the participant should not be randomized until the test has been repeated.

Contamination Codes: Record the appropriate code for each used pad.

Code	Description
Record 01	if the pad is **not contaminated** with anything other than urine.
Record 02	if the pad is **soaked through** with urine.
Record 03	if the pad is contaminated with blood.
Record 04	if the pad is contaminated with stool.
Record 05	if the pad is contaminated with blood and stool.
Record 06	if the pad is soaked through with urine **and** contaminated with blood.
Record 07	if the pad is soaked through with urine **and** contaminated with stool.
Record 08	if the pad is soaked through with urine **and** contaminated with blood **and** stool.
Record 09	if you cannot identify the contaminant.

If Kits are returned with some pads missing:

Other Codes

Record 10	if the pad is missing and the participant reports that she **DID NOT USE** the pad during the 24-hour testing period.
Record 11	if the pad is returned and **NOT USED**.
Record 12	if the pad is missing and the participant reports that she **DID USE** the pad during the 24-hour testing period. This error will invalidate the test and the test should be repeated. Refer to the Operations Manual or call the CC for directions.

7. **Date Kit Returned:** Record the date the Pad Test Kit is returned. This should be the same date as the date the post-weight measurements are completed.

Note: If more than 10 pads are requested or used please use the Pad Test Auxiliary data form. The date of visit in the banner should be the same as the date of visit on the Pad Test form.

12.3.3 Completion of On-site Questionnaires

Seat the participant comfortably in a quiet room with a clean writing surface. Give her a black ball-point pen and ask her to fill out the Randomization Visit questionnaires while she is at the clinic. Review each questionnaire for completeness when she is finished.

12.3.3.1 UI Symptoms Questionnaire (9 pages)

The Urinary Incontinence Symptoms questionnaire explores in detail the extent and severity of symptoms of urinary incontinence experienced by the participant. Questions 1 – 11, 15 and 15a refer to the participant's experiences in the **past month**. Question 14 refers to a **typical week** and question 16 to a **typical day**. The questions are self-explanatory but you may help the participant interpret a question if necessary. If she says she is uncertain about how to respond ask her to use her best estimate. If she insists she can't remember then leave the response blank.

12.3.3.2 Urogenital Distress Inventory (2 pages)

This is a brief questionnaire that focuses on how bothersome urinary incontinence is to the participant. For each item in question 1, either the "No" or the "Yes" bubble should be marked. If the response is "No", go to the next item. If the response is "Yes", choose one of the bubbles to the right that grades the degree of bother.

Remind participants to answer question 2. They are asked to choose the one symptom from the list (A – T) in question 1 that has been most bothersome. The letter of the symptom should be entered in the box.

12.3.4 Weight and Abdominal Circumference

Ask the participant to remove her shoes and anything in her pockets. Weigh her in kilograms twice on the Tanita BWB 800 digital scales, following the detailed directions in Chapter 14.1.4 (Physical Measurements). Calculate the average of the two measurements and record all results on the WEIGHT/ABDOMINAL CIRCUMFERENCE data form.

Ask the participant to lift her blouse and measure the circumference of her waist with the Gulick tape according to the detailed procedures in Chapter 14.1.5. Remove the tape and make a second measurement. Record all results on the WEIGHT/ABDOMINAL CIRCUMFERENCE data form. Calculate the difference between the measurements using the calculator. If the difference between Measurement 1 and Measurement 2 is equal to or greater than 1 cm

make a third measurement and record it on the data form.

12.3.5 Distribution of Urinary Incontinence Handbook

At the end of the visit present each participant with the PRIDE "Staying Dry" handbook. This booklet provides useful information about hygienic means to controlling urinary incontinence. The following is the suggested script to use when presenting the booklet:

"As part of your participation in the PRIDE project, we would like to offer you this booklet called Staying Dry: A Practical Guide to Bladder Control. This is a self-help booklet with instructions to guide you through a step-by-step program designed to improve bladder control. It was developed through many years of research and has proven beneficial for many women with incontinence."

Briefly review the sections that describe the Kegel exercises and suggest that the participant do these exercises in addition to her group activities at the clinic.

12.3.6 Randomizing the Participant

Review all inclusion/exclusion criteria to be sure the participant still qualifies for the study. Ask the participant if she has started any new medications since her last visit and ensure that, if she has, the medications are not exclusionary. All Inclusion criteria must be marked "Yes" and all Exclusion criteria must be marked "No" in order to proceed.

Take the next numbered randomization envelope from the correct stack, according to whether or not the participant has taken part in the urodynamic study. Complete questions 3 and 4 on the Randomization Inclusion/Exclusion form and enter the participant's randomization number.

12.3.6.1 Randomization Log

Each clinical center should keep a log of all participants randomized. This will be referred to as the PRIDE Randomization Log Sheet (See Appendix 12B). The PRIDE Randomization Log Sheet will be for clinic use and organization only, and will not be entered into the PRIDE database. This log should contain at least the following information: (1) Randomization Number (2) ID number and Acrostic;;

and (3) the date the candidate was randomized. The PRIDE Randomization Log Sheet links the study ID to the Randomization Number. Update the log each time a participant is randomized, making sure that the randomization numbers follow in the correct sequence.

12.4 RANDOMIZATION ERRORS

Occasionally the clinic or the Coordinating Center uncovers information that indicates that a randomized participant was not eligible. One reason for this is that a participant may not have revealed information that made her ineligible until after the randomization. Alternatively, a data entry error may have been made, leading her to be considered eligible and subsequently to be randomized in error.

When a randomization error is known to have occurred: (1) a memorandum signed by the Study Coordinator and Principal Investigator should be sent to the Coordinating Center as soon as the situation is uncovered; and (2) the participant remains a part of the PRIDE study. The Coordinating Center will monitor the frequency and type of randomization errors and report them regularly to the Data Safety Monitoring Board.

Appendix 12A

Inclusion/Exclusion Criteria

Inclusion Criteria:	**Form:**
A. Is the participant aged ≥ 30 years?	Demographics Form
B. Does the participant have a body mass index of 25 to 45 kg/m^2?	Height/Weight Form
C. Has the participant experienced urinary incontinence symptoms for ≥ 3 months with ≥ 10 incontinent episodes per week on a 7-day urinary diary?	First 7-Day Voiding Diary, Voiding Diary Data Form
D. Is the participant able to complete a behavioral run-in consisting of self-monitoring of food and activity?	7-Day Food and Exercise Diary
E. Does the participant have a primary health care provider?	Eligibility Screening Form, Contact Information (local)
F. Can the participant understand and complete self-administered questionnaires?	Screening Questionnaires
G. Has the participant agreed not to initiate a new treatment for incontinence or weight reduction, including behavioral, pharmacological or surgical therapies, for the duration of the study?	Informed Consent Signed
H. Has the participant signed an informed consent?	Informed Consent Signed
I. Has the participant completed all necessary screening measures and forms?	Screening Checklist, Randomization Checklist
J. Is the participant unable to walk 2 blocks without stopping and without a cane or walker?	Eligibility Screening Form
Exclusion Criteria:	**Form:**
A. Is the participant currently using medical therapy for incontinence or weight loss?	Eligibility Screening Form, Medications Form
B. Is the participant currently engaged in an active weight loss program and/or experienced a 10 lbs or greater weight reduction in the past 3 months?	Eligibility Screening Form
C. Is the participant currently pregnant or has she given birth in the past 6 months?	Eligibility Screening Form
D. Does the participant currently have a urinary tract infection or report having ≥ 4 urinary tract infections	Eligibility Screening Form, Dipstick Urinalysis

in the past year?	Form
E. Does the participant report incontinence of neurologic or functional origin?	Health History
F. Has the participant reported any prior anti-incontinence or urethral surgery, pelvic cancer, or pelvic irradiation?	Eligibility Screening Form, Health History
G. Has the participant reported any significant medical conditions of the genitourinary tract?	Health History
H. Does the participant have any medical conditions that would affect the safety of the study (type 2 diabetes, uncontrolled HTN, etc)?	Eligibility Screening Form, Medications, Health History, Vital Signs
I. Has the participant reported any conditions that, in the judgment of the Clinical Center Principal Investigator, render her unlikely to follow the protocol for 18 months, including illness likely to be terminal within 2 years, plans to move, substance abuse or other significant psychiatric problems or dementia?	Eligibility Screening Form, Medications Form, Health History, Beck Depression Index
J. Is the participant participating in another research study that involves investigational drugs or that can potentially confound the results of PRIDE?	Eligibility Screening
K. Is the participant institutionalized?	Contact Information (local)

Appendix 12B

Example PRIDE Randomization Log Sheet

PRIDE Randomization Log Sheet

Randomization Number	Participant ID	Acrostic	Date of Randomization
X001	*50001*	ABCD	01/01/2000
X002			
X003			
X004			
X005			
X006			
X007			
X008			
X009			
X010			
X011			
X012			
X013			
X014			
X015			

`CHAPTER 13

FOLLOW-UP VISITS

13.0 FOLLOW-UP VISITS

13.1 OVERVIEW

At 6, 12 and 18 months, participants will visit the clinical centers for repeat weight and waist measurements, vital signs, 7-day voiding diary, pad test and various health and behavioral assessment questionnaires. At the site's discretion, questionnaires can be mailed to participants 3 weeks before the follow-up visits. Participants will complete these questionnaires at home and return them at their visit to be reviewed by study staff. The voiding diary and pad test kit will be given to participants at the visit and they will be asked to mail these back after completing them. Participants will be asked to bring to the visit all prescription and non-prescription medications they are currently taking, and these will be recorded. Their health status will be reviewed.

Ideally, the follow-up Urodynamic Substudy (UDS) visits should take place prior to the 6 month clinic evaluation. However, if this is impossible to schedule, the UDS visit should take place as close after the Month 6 follow-up visit as possible.

13.2 PREPARATION FOR THE VISIT

If an appointment was not scheduled at the previous visit, the participant should be contacted at least one month prior to the target date to schedule the follow-up visit. Reminder calls, letters or postcards can be sent to help avoid no-shows and to provide some information about the visit.

Let the participant know that this visit is different from the classes or sessions in which she has been participating and let her know the approximate length of the visit. Ask her to bring with her all the prescription and non-prescription medications that she takes regularly. In order to maintain the blind, remind the participant that she should not discuss her group assignment with any of the staff during the clinic visit.

Several of the self-administered questionnaires may be mailed ahead of time so that the participant can complete them at home and bring them with her to the visit. The Beck Depression Inventory should not be mailed, but should be completed and reviewed during the visit.

Forms/Procedures Needed for Month 6 Visit

- 6-Month Checklist
- Weight and Abdominal Circumference
- Vital Signs
- Concurrent Medications
- Serious Adverse Event Form (if needed)
- Food Frequency Questionnaire
- Incontinence Impact Questionnaire (IIQ)
- UI Symptoms
- Urogenital Distress Inventory (UDI)
- Paffenbarger Activity Questionnaire
- Short form – 36
- Sleep Questionnaire
- Sexual Function Questionnaire
- Bowel Habits
- Beck Depression Inventory
- Participant Satisfaction Questionnaire*
- Pelvic Muscle Questionnaire*
- Health Utilities
- Cost Analysis (Follow-up*
- Motivation Questionnaire (Follow-up)*
- 7-Day Voiding Diary
- 24-Hour Pad Test Kit
- Randomization to Maintenance Group

* These questionnaires are being administered for the first time.

Please have a calculator available.

13.3 MONTH 6 PROCEDURES

13.3.1 Vital Signs

Measure the participant's blood pressure and pulse using the Dinamap Monitor Pro 100 according to the instructions in Chapter 14.2. Enter the results on the VITAL SIGNS data form.

13.3.2 Weight and Abdominal Circumference

Ask the participant to remove her shoes and anything in her pockets. Weigh

her twice in kilograms on the Tanita BWB 800 digital scales, following the detailed directions in Chapter 14.1.4 (Physical Measurements). Calculate the average of the two measurements and record all results on the WEIGHT/ABDOMINAL CIRCUMFERENCE data form.

Ask the participant to lift her blouse and measure the circumference of her waist with the Gulick tape according to the detailed procedures in Chapter 14.1.5. Remove the tape and then make a second measurement. Record all results on the WEIGHT/ABDOMINAL CIRCUMFERENCE data form. Calculate the difference between the measurements using the calculator. If the difference between Measurement 1 and Measurement 2 is equal to or greater than 1 cm make a third measurement and record it on the data form.

13.3.3 Concurrent Medications and Serious Adverse Events

Ask the participant if she has seen her doctor, been hospitalized or experienced any serious health events in the past six months. Any events that meet the definition of "Serious Adverse Event" (SAE), described in Chapter 17 of the PRIDE Operations Manual, must be reported to your IRB and documented on the SAE Form. Please note that SAEs should be reported as soon as you are made aware of them. This follow-up visit provides an additional occasion to check for events that may have happened to participants you haven't seen frequently. The responses to questions 1 and 2 on the Cost Analysis form may be a cue to probe further for SAEs as well, however, these questions relate only to the past three months. Please review all self-administered questionnaires before the participant leaves the site. If you are uncertain whether a medical visit or health event qualifies as an SAE, please contact the Coordinating Center for advice.

Ask the participant if she has had any changes in prescription medications, or started or stopped medications. Check to see if she has started or stopped over-the-counter medications also. The participant should bring to the visit all prescription and non-prescription medications that she takes on a regular basis. Look at each medication and record either the trade name (preferably) or the generic name of each medication, but not both. Record over-the-counter medications only if they are taken on a regular basis.

Please record all medications even if there has been no change since baseline.
If the participant is not taking any medications regularly, print "NONE" in the

boxes after "1. Trade Name."

13.3.4 Questionnaires

Most questionnaires have been administered previously during screening or randomization visits and instructions for each can be found in Chapter 10 or Chapter 12. The Beck Depression Inventory must be completed and reviewed on-site. It might be helpful to complete the Paffenbarger on-site so that staff can assist the participant. As during screening, the Sexual Function questionnaire should be accompanied by a stamped, addressed envelope, completed off-site and sent directly to the Coordinating Center. Whether other questionnaires are completed on- or off-site is left to the discretion of study staff. All questionnaires to be completed off-site should be mailed to the participant in advance so that she can complete them at home and bring them with her to the clinic visit. Please check the list at the beginning of Section 13.2 to be sure you have administered all questionnaires.

The following questionnaires are administered for the first time at this visit.

13.3.4.1 Participant Satisfaction Questionnaire

This one page form is designed to assess in general terms the participant's perception of changes in her incontinence. Note that the questions ask her, at each of the follow-up visits, to compare her current experience with her pre-PRIDE experience.

13.3.4.2 Pelvic Muscle Questionnaire

The two page Pelvic Muscle Questionnaire is designed to elicit information about the extent to which all participants practice the exercises that are described in the "Staying Dry" handbook.
If the response to question 1 is "Didn't receive the booklet" the participant should not answer any of the other questions. If she forgot she had the booklet, lost it right away or claims she never received one she should mark this first response. PLEASE GIVE THE PARTICIPANT A BOOKLET AT THIS TIME if she doesn't have one.

If the response is "Haven't read the booklet" the participant should complete the questionnaire. It is possible that she may have received instructions about the pelvic muscle exercises from a different source

and may be practicing them anyway. Primarily, we want to know whether she is doing pelvic muscle exercises, regardless of the source of her information.

13.3.4.3 Cost Analysis (Follow-up)

The Cost-Analysis (Follow-up) questionnaire is an expanded 8 page version of the baseline questionnaire. Please be sure you have printed the correct version. Ensure that all questions are answered and the skip patterns are followed. If the response to question 1a, 1c or 1d is greater than 0 be sure to ascertain whether or not the participant has had a serious adverse event.

13.3.4.4 Motivation Questionnaire (Follow-up)

The Motivation Questionnaire (Follow-up) has several questions that are different from baseline. Please be sure you have printed the correct version. Ensure that all questions are answered according to instructions and that skip patterns are followed.

13.4 7-DAY VOIDING DIARY AND 24-HOUR PAD TEST

Review the instructions for the 7-day Voiding Diary and the 24 hour Pad Test carefully with each participant during the visit, according to the description in Chapters 9.3.3 and 10.4.2.8 of the Operations Manual (OM). If the participant claims to remember the instructions, praise her for doing so but probe a little further for detail, for example: "Are you clear about the difference between an urge episode and a stress episode of incontinence? That can be pretty confusing at times." Give her the printed instructions for each test to take home. Give the participant the long or short form of the 7-day Voiding Diary, depending on the number entries she made during the screening phase. Offer her the new compact size diary only if the size of the original diary was a problem for her in the past, and only if she uses the short form of the diary. (The compact version does not have as many pages as the long version of the diary.)

Provide a self-addressed, pre-paid UPS mailer that will hold both the Pad Test kit and the diary. Ask the participant to complete the diary and the pad test in the week following her visit, and to mail the pads and diary back to you as soon as they have been completed. If it is inconvenient for the participant to complete the diary and pad test the next week, determine when she will start the diary and schedule a reminder call to her the day before. Optimally, the pad test should be completed for a 24-hour

period during the same week that the 7-day voiding diary is completed.

When the diary and pads are returned, review both for accuracy and completeness. The diary review should be done according to the instructions in Chapter 10.3.2.2 of the OM. Complete the Voiding Diary Data Entry form according to the instructions in Chapter 10.3.2.3. During follow-up, failure to complete the diary properly does not disqualify the participant from PRIDE. However, this is the primary outcome data and every effort should be made to ensure that the dairy is completed properly for at least five out of seven days. If this requirement is not met, offer to mail another diary immediately and ask the participant to try to fill the diary out again. Discuss any issues that may have impacted her ability to follow the instructions.

Weigh the pads as soon as you receive them and fill out the rest of the Pad Test form according to the instructions in Chapter 10.4.2.8.7 of the OM. If the participant has forgotten to fill out the labels on the bags containing the pads please call her to obtain the correct information.

When all procedures and forms, including the 6 month checklist, have been completed, fax them to the data system at the Coordinating Center.

13.5 RANDOMIZATION TO WEIGHT MAINTENANCE PROGRAMS

The weight loss intervention groups will be assigned randomly to either a motivation-based or a skills-based motivation program. The random assignment will be made just before the final session of the weight loss intervention program. The study coordinator or interventionist will contact the project assistant at the Coordinating Center to receive, by e-mail, the maintenance phase assignment for each intervention group. Study center staff will send an email back to the Coordinating Center confirming assignment of the maintenance groups. Participants will not be informed of the group assignments.

13.6 MONTH 12 VISIT

13.6.1 Preparation for the Visit

If an appointment was not scheduled at the previous visit, the participant should be contacted at least one month prior to the target date to schedule the follow-up visit. Reminder calls, letters or postcards can be sent to help avoid no-shows and to provide some information about the visit.

Let the participant know that this visit is different from the classes or sessions in which she has been participating and let her know the approximate length of the visit. Ask her to bring with her all the prescription and non-prescription medications that she takes regularly. In order to maintain the blind, remind the participant that she should not discuss her group assignment with any of the staff during the clinic visit.

Several of the self-administered questionnaires may be mailed ahead of time so that the participant can complete them at home and bring them with her to the visit. The Beck Depression Inventory should not be mailed, but should be completed and reviewed during the visit.

Forms/Supplies Needed for Month 12 Visit

- 12-Month Checklist
- Weight and Abdominal Circumference
- Vital Signs
- Concurrent Medications
- Serious Adverse Event Form (if needed)
- Food Frequency Questionnaire
- Incontinence Impact Questionnaire (IIQ)
- UI Symptoms
- Urogenital Distress Inventory (UDI)
- Paffenbarger Activity Questionnaire
- Short form – 36
- Sleep Questionnaire
- Sexual Function Questionnaire
- Bowel Habits
- Beck Depression Inventory (complete in clinic)
- Participant Satisfaction Questionnaire
- Pelvic Muscle Questionnaire
- Health Utilities Index
- Cost Analysis (Follow-up)
- Motivation Questionnaire (Follow-up)
- 7-Day Voiding Diary
- 24-Hour Pad Test Kit
- Month 12 Participant Thank You gift – gym bag

Please have a calculator available.

13.6.2 Vital Signs

Measure the participant's blood pressure and pulse using the Dinamap Monitor Pro 100 according to the instructions in Chapter 14.2. Enter the results on the VITAL SIGNS data form, marking the Month 12 bubble.

13.6.3 Weight and Abdominal Circumference

Ask the participant to remove her shoes and anything in her pockets. Weigh her twice in kilograms on the Tanita BWB 800 digital scales, following the detailed directions in Chapter 14.1.4 (Physical Measurements). Calculate the average of the two measurements and record all results on the WEIGHT/ABDOMINAL CIRCUMFERENCE data form, marking the month 12 12bubble.

Ask the participant to lift her blouse and measure the circumference of her waist with the Gulick tape according to the detailed procedures in Chapter 14.1.5. Remove the tape and then make a second measurement. Record all results on the WEIGHT/ABDOMINAL CIRCUMFERENCE data form. Calculate the difference between the measurements using the calculator. If the difference between Measurement 1 and Measurement 2 is equal to or greater than 1 cm make a third measurement and record it on the data form.

13.6.4 Concurrent Medications and Serious Adverse Events

Ask the participant if she has seen her doctor, been hospitalized or experienced any serious health events in the past six months. Any events that meet the definition of "Serious Adverse Event" (SAE), described in Chapter 17 of the PRIDE Operations Manual, must be reported to your IRB and documented on the SAE Form. Please note that SAEs should be reported as soon as you are made aware of them. This follow-up visit provides an additional occasion to check for events that may have happened to participants you haven't seen frequently. The responses to questions 1 and 2 on the Cost Analysis form may be a cue to probe further for SAEs as well, however, these questions relate only to the past three months. Please review all self-administered questionnaires before the participant leaves the site. If you are uncertain whether a medical visit or health event qualifies as an SAE, please contact the Coordinating Center for advice.

Ask the participant if she has had any changes in prescription medications, or

started or stopped medications. Check to see if she has started or stopped over-the-counter medications also. The participant should bring to the visit all prescription and non-prescription medications that she takes on a regular basis. Look at each medication and record either the trade name (preferably) or the generic name of each medication, but not both. Record over-the-counter medications only if they are taken on a regular basis.

Please record all medications even if there has been no change since the previous visit.
If the participant is not taking any medications regularly, print "NONE" in the boxes after "1. Trade Name."

13.6.5 Questionnaires

All questionnaires were administered previously at the Month 6 visit and instructions for each can be found in Chapters 10, 12 or Chapter 13.3.4 . The Beck Depression Inventory must be completed and reviewed on-site. It might be helpful to complete the Paffenbarger on-site so that staff can assist the participant. As before, the Sexual Function questionnaire should be accompanied by a stamped, addressed envelope, completed off-site and sent directly to the Coordinating Center. Whether other questionnaires are completed on- or off-site is left to the discretion of study staff. All questionnaires to be completed off-site should be mailed to the participant in advance so that she can complete them at home and bring them with her to the clinic visit. Please check the list at the beginning of Section 13.6 to be sure you have administered all questionnaires.

13.7 MONTH 18 VISIT

Forms and procedures for the Month 18 visit are the same as those described for Month 12 (Chapter 13.6) with the addition of the Exit Questionnaire. As always, please make every effort to obtain physical measurements, voiding diaries and pad tests for all participants in addition to the questionnaires.

At the end of the visit be prepared to inform the participant about the group end-of-study celebration at which time she will hear more about incontinence. Be prepared to inform the participant about when and how she will receive results of the study when all participants are finished and the data analysis is completed. Update contact information if necessary.

Thank the participant for the contribution she has made and present her with the end of study gift.

13.7.1 Exit Questionnaire

Three Exit Questionnaires have been developed to assess the participant's opinion of the PRIDE Structured Education Program, Skills-based Maintenance Program, and Motivation-based Maintenance Program. The Structured Education Exit Questionnaire has one question, while the Skills-based Maintenance Program and Motivation-based Maintenance Program Questionnaires have several questions divided into Section I (maintenance in general) and Section II (program specific content). For each participant, please be sure you have printed the correct version. Ensure that all questions are answered according to instructions.

13.8 TECHNIQUES FOR ENHANCING COMPLIANCE

The following is a list of ideas that may be used to encourage compliance or to prevent drop-outs.

Personal Contact: Focus on the participant and make her experience in the study a personal one. While it is good to share a little of your own life in forming a bond, the primary focus should be the participant, her life and interests and in particular, the support or lack of support that she receives from family and friends for the PRIDE program.

Each site should take advantage of the personal bond that PRIDE participants may develop with PRIDE staff members, or with the group to which they've been assigned. Try to achieve continuity of participant-staff contact. If a staff member who has developed a good relationship with the participants must leave PRIDE, the transition should be announced to participants. New PRIDE staff members should be introduced to all participants by telephone or mail, preferably by the departing staff member.

Schedule Visits and Provide Reminders: At the end of each visit, schedule the next, so that you are aware, early on, of extended vacations or changes in work schedules, for example, that may impact participation. Ask the participant to mark her calendar. Send reminder cards or make reminder phone calls about one month before the visit and alert participants that a packet of questionnaires will be arriving in the mail.

Update Contact Information: The participant's life situation could change significantly

during the time she is in PRIDE. Ask for information on alternative contact persons, usually family members, who could help you find the participant if necessary. Update this information at each visit. Ask the participant for the names of doctors she sees regularly and keep this up-to-date as well. The physician's office may be able to provide useful information when tracking participants who become lost to follow-up. Ask the participant to let you know if ever she is hospitalized. You can then file a Serious Adverse Event report in a timely manner, and send her a get-well card!

Cards, Letters, and Gifts: Send cards to confirm appointments. Send birthday cards. Provide small "thank you for participating" gifts (e.g. small packs of personal greeting cards). Make an interim phone call if necessary, particularly to those in the education group who aren't seen frequently, just to maintain contact and keep abreast of developments in the participant's life that may affect her participation.

Collaborate with Colleagues: Share your compliance experiences. Each site has a different mix of participants, and together you can develop solutions to problems you may encounter. The Coordinating Center will promote exchanges of such experiences during the Coordinators conference calls. The Coordinating Center will also provide ongoing feedback to sites from the Participant Satisfaction questionnaires.

13.9 PREMATURE DISCONTINUATION FROM PRIDE

Every effort should be made to persuade participants to remain in the study regardless of their ability to comply with the study procedures. At the very least, they should be encouraged to attend the 6, 12 and 18 month follow-up visits where outcome measures can be recorded. Participants who are unresponsive to at least three calls from study personnel should be contacted personally by the Principal Investigator.

Every participant has the right to withdraw from the study at any time. On those rare occasions when a participant exercises this right clearly and explicitly, follow-up must be discontinued as of that date. If appropriate, you may let the participant know that she is welcome to return to the study at ay time.

Generally, the data forms will capture lack of adherence to any of the study procedures. However, if it is determined that the participant will never return for outcome measurements, a Termination Report must be filled out and faxed to the data system. Please mark the bubble that would have represented the participant's next visit. In question 1, enter the date when the participant told you she had decided to drop out of the study. For question 2, please choose the primary reason for early

discontinuation. Once the Termination report has been filed, the "missing forms" queries will be removed from the data system.

13.10 CHANGE OF STATUS

On those rare occasions when a discontinued participant elects to rejoin the study, a Change of Status Form must be filled out and faxed to the data system. Fill in the bubble for question 1. In Question 1A, enter the date when the participant told you she had decided to rejoin the study. For question 1B, please choose the primary reason for resuming participation. Once the Change of Status Form has been filed, the participant can resume study visits.

If a participant elects to discontinue the study for a second time, she may not rejoin the study at a future date and a Change of Status Form must be filled out and faxed to the data system. Fill in the bubble for question 2. In Question 2A, enter the date when the participant told you she had decided drop out of the study again. For question 2B, please choose the primary reason for early discontinuation. Once the Change of Status Form has been filed, the "missing forms" queries will be removed from the data system.

CHAPTER 14

PHYSICAL MEASUREMENTS

14.0 PHYSICAL MEASUREMENTS

14.1 HEIGHT, WEIGHT AND ABDOMINAL CIRCUMFERENCE

14.1.1 Overview of Body Size Measurements

Equipment used for body size measurements in PRIDE will be the same equipment used in the Look AHEAD study. Procedures are similar also but the measurement units may be different in PRIDE and the instructions should be reviewed carefully before measurements begin.

Change in body weight is a primary measure of effectiveness of the interventions in this trial. Body weight relative to height, expressed as Quetlet's index, or body mass index (BMI, kg/m^2), is an index of fatness highly correlated with more direct measures of body fat. Abdominal (waist) circumference and changes in waist circumference are indicators of subcutaneous and visceral fat deposits in the abdominal region.

Participants should wear light clothing, e.g., a short sleeve shirt or blouse (or surgical gown), shorts, socks but remove shoes (for weight and height) and items in pockets. A supply of gowns should be maintained at the clinic for participants who forget to wear or bring the appropriate clothes for body size measurements.

Staff who are masked to the intervention assignment of the participant should make body size measurements. If possible, a team of two people, one acting as observer and the other as recorder, should perform the measurements. The observer takes the measurements, reporting the results to the recorder, who repeats them. The observer keeps the measuring instrument in place until the recorder repeats the number. The recorder generally checks the participant's position during the procedure. If a second observer is not available, a mirror can be used to check for the correct position (e.g., whether the tape is horizontal for waist circumferences). Have a calculator available for the required calculations or complete the calculations after the visit is over and before faxing the form to the Coordinating Center.

Height and weight will be measured during screening and BMI will be calculated to determine eligibility. Weight and abdominal circumference will be measured at the randomization visit and at months 6, 12 and 18. Weight only will be measured at month 3.

14.1.2 Body Height

A wall-mounted stadiometer graduated in centimeters with a horizontal measuring block (or fixed angle) is to be used. If the stadiometer is not wall-mounted, you will need a level to ensure that the horizontal measuring block is level.

Ask the participant to stand with her back against the wall-mounted stadiometer, heels together. The back (scapulae), buttocks and both heels should be touching the wall-plate. Note: the participant should be standing with head erect and in the Frankfort horizontal plane (see below), but, in general, the back of the head does not need to be in contact with the wall-plate. Her arms should be relaxed and hanging loosely at her sides with shoulders relaxed.

The head should be in the "Frankfort Horizontal Plane". That is, the lowest point on the inferior orbital margin (orbitale) and the upper margin of the external auditory meatus (tragion) form a horizontal line (Figure 1).

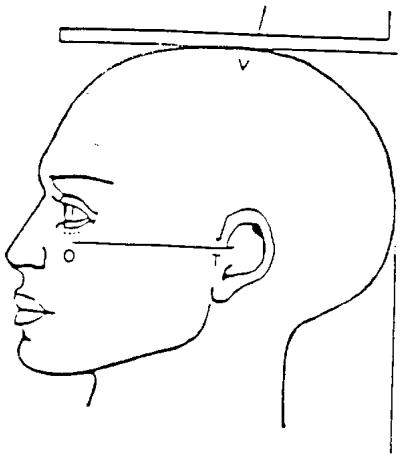


Figure 1.
Orbitale: Lower margin of eye socket
Tragion: Notch above tragus of ear
Frankfort plane: Orbitale-tragion line horizontal

Be sure that the participant maintains the correct posture during the measurement.

Bring the horizontal measuring block down snugly, but not tightly, on the top of the head.

Measure the participant's height to the nearest centimeter. Divide by 100 to get the height in meters and record the measurement on the Height/Weight data form as Standing Height: item #1.

Ask the participant to step away, raise the measuring block and repeat the procedure. Record this as Standing Height: item#2.

Calculate the average of the two measurements {(measurement 1 + measurement 2) / 2} and enter the result in Standing Height: item #3.

14.1.2.1 Deviations and exceptions to standard positioning

Obese participants and those with a kyphotic posture may not be able to place the heels, buttocks, and scapulae in a single vertical plane while maintaining a reasonable natural stance. These participants may be positioned so that only the buttocks, and possibly the scapula, are in contact with the wall-plate. The essential point is that the participant stand erect with the buttocks in contact with the wall plate and the legs as close together as possible. In very obese participants, if it is not possible to obtain contact between the headboard and the top of the skull, then the participant may need to lean back slightly (without tilting the head) until proper contact can be made.

For participants with severe spinal curvature, if the spine is the part that protrudes the farthest, then that should be the part that is touching the wall plate, together with heels and buttocks.

For participants with extreme kyphotic posture, it may not be possible to obtain contact between the headboard and scalp when the participant's back is against the wall-plate. In this case, measure height with the participant standing sideways (side of arm and shoulder in contact with the wall-plate) and positioned so that the headboard contacts the scalp. The head should be in the Frankfort Horizontal Plane.

If the participant has 'knock-knees' then have her separate the heels so that the knees are in contact but do not overlap. Obese participants may also not be able to stand comfortably with the heels touching and may stand with the legs together and the heels separated.

14.1.3 Calibration Procedures for Stadiometer

Calibration of the stadiometer should be done before any measurements are done for PRIDE and then once a month. Place a metal rod of 1 meter length between the headboard and the floor so that it stands vertically. Record the measurement on the "Monthly Stadiometer Calibration Log" (Appendix 14A).

If the stadiometer does not record the correct length of the rod it must be re-positioned on the wall until an accurate measurement is recorded. Move the headboard up and down the backboard a number of times to ensure that a consistently accurate reading can be made.

14.1.4 Body Weight

Weight should be measured on Tanita BWB 800 digital scales (Tanita Corp., Arlington Heights, IL) set to be read in kilograms. Efforts should be made to weigh each participant under conditions as similar as possible on all visits (e.g., same time of day, limited consumption of fluids).

The participant should be asked to remove shoes and contents of pockets and to stand still in the middle of the scale platform with head erect and eyes looking straight ahead. Record the weight in kilograms to the nearest 0.1 kg as indicated on the digital display. During Screening, record this as Weight; item#4 on the Height/Weight form. Ask the participant to step off the scale and check that the digital display returns to zero. Repeat the measurement and record the weight as Weight; item#5 on the Height/Weight form. Calculate the average of the two measurements {(measurement 1 + measurement 2) / 2} and enter the result in item #6.

When weight is taken at randomization and all follow-up visits, the measurements should be recorded on the Weight/Abdominal Circumference data form as items #1, #2 and the average, item #3.

14.1.4.1 Quality Control for Weight Scale

The scale must be positioned on a level floor. Never drop a weight on, or subject the scale platform to shock loading and do not store equipment or weights on the platform. Moving of scales should be avoided, and calibration should be rechecked after moving a scale to a new location.

14.1.4.2 Weekly Calibration Checks

Calibration checks will be carried out prior to the weighing of the first participant at the start of the study, at least weekly thereafter so long as participants are scheduled for measurement visits, and before weighing a participant after a period of time greater than one week during which no weight measurements were made. At each calibration, values will be recorded in a log maintained for this purpose (see Appendix 14 B). The log will be reviewed during site visits.

The tolerance on a scale capable of weighing up to 200 kg is $\pm$ 0.1 kg (one scale division). Deviations of more than one scale division will require corrective action; specifically, the scale must be shipped to the manufacturer for calibration. Contact Tanita Technical Assistance at 1-877-682-6482. Tanita will provide you with an authorization number and instructions on shipping the scale.

14.1.4.3 Calibration Procedure

The calibration procedure for the scales will be identical to those performed for the Look AHEAD study. Calibration checks should be carried out on equipment in its normal location. A class F certified 20 kg calibration weight will be used for checking scale calibration. The calibration weights should be stored and used according to manufacturer's instructions (which should be saved and filed along with accompanying certificates).

The calibration weights should be stored on the floor against the wall near the scale, NOT on an elevated surface. This will keep carrying the weights to a minimum. Staff should review the recommended

procedures for lifting heavy objects (bend at the knees, keep back straight, etc.) Sites might assign a staff member who is more physically capable to do the calibration on a regular basis. Finally, the 20 kg weight could be replaced with two calibrated 10 kg weights. A good procedure for placing the calibration weight is to put the weight in the center of the scale platform leaving some room at the edges for the feet.

The following procedure checks the repeatability of readings and the linearity of the scale in a portion of the working range.

1. Place the 20 kg weight (gently) on the scale platform. Record the weight indicated on the scale.
2. Remove the weight from the scale platform and allow the display to return to zero.
3. Step (or have an assistant step) on the scale. Record the weight indicated on the scale.
4. Step off the scale. Allow the display to return to zero.
5. Have the assistant step on the scale platform while holding the 20 kg weight. Record the scale reading.
6. Step off the scale. Allow the display to return to zero.

Repeat the six steps above at least once, and then compare the values obtained.

If the repeated weighing of the calibration weight, or the assistant's weight, or the weight of the assistant plus the calibration weight do not yield the same values each time, or, if the weight of the assistant plus the calibration weight is more than 0.1 kg different from the sum of the two weighed individually then the scale is probably faulty. Contact Tanita (as described above) for instructions on how to ship the scale to them for calibration.

Results of the above tests should be recorded in the calibration log, signed and dated by the person performing the calibration, and the form will be retained as part of the study documentation. If the tests indicate that the equipment is out of tolerance or faulty, the nature of the deviation and the action taken should be noted as a comment on the calibration form.

14.1.4.4 Annual Commercial Calibration

Annually, beginning one year from the date a new scale is placed into service, or if the scale is not new, before the date the scale is placed into service and annually thereafter, a commercial calibration contractor or the manufacturer of the scale (Tanita) shall be engaged to certify the calibration of the scale. See information above for contact with Tanita (1-877-682-6482). Calibration must be carried out with a sufficient number of test weights to load the machine at four or more points across its working range. A calibration certificate should be issued by the commercial contractor that includes:

- the date of calibration
- serial number of the scale
- test weights used and scale readings at those test weights
- deviations observed at each load
- the nature of any adjustments or corrections made to the scale (i.e., before/after readings)
- name and signature of the technician who carried out the calibration

This certificate will be kept in the log along with the record of weekly site staff calibrations.

14.1.5 Abdominal Circumference

The Gulick II Tape Measure (model 67020) will be used to measure waist circumference. The design of the tape measure eliminates guesswork by applying a known amount of tension (four ounces) to the measuring tape. When used properly, tape tension is always four ounces. Therefore, accurate measurements are possible no matter who is doing the measuring.

To take measurements: Pull an appropriate amount of tape out of the housing. Wrap the tape once around the waist (see instructions below). Align the tape's "zero line" along side of the tape graduations. Use the Metric units (cm). Now simply pull on the end of the tensioning mechanism until the **calibration point** is just seen. Read the measurement next to the tape's "zero line".

What is meant by "calibration point": When you pull slightly harder and harder on the tensioning device, two colored beads will be seen separated by a

silver disk. When you are pulling with exactly 4 ounces of force, you will see a silver disk separating the two beads. When you see one of the two beads, you are at the "calibration point". Remember, four ounces is not a great deal of force, in fact, it is approximately equal to the force required to lift a stack of 20 U.S. quarters. So don't pull so hard that the beads start to disappear into the end cap of the tensioning device. That is too much force.

Ideally, waist circumference would be measured in the morning after voiding. If this is not possible efforts should be made to measure each participant under conditions as similar as possible on all visits (e.g., same time of day, limited consumption of fluids).

Ask the participant to stand with feet together. Take the measurement around the abdomen horizontally at midpoint between highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line. Mark the midpoint on both sides using a washable marker. (The participant may be asked to assist passing the tape around the abdomen by holding the end of the tape in position). (If the tape cannot be made horizontal across the waist markings, default to the right hip.) When the tape is positioned in the horizontal plane at the correct height, the participant should be asked to keep her arms at her side and breathe in and out naturally, holding at the end of a normal exhalation. Record the circumference to the nearest 0.1centimeter. Enter the measurement on the Weight/Abdominal Circumference data form as Abdominal Circumference; item #4. Remove the tape and repeat the procedure recording the second measurement on the same form as item #5. Subtract measurement 2 from measurement 1 and enter the absolute difference in item #6. If the number in item#6 is 1 cm or more, repeat the measurement a third time and record the result in item #7.

14.1.5.1 Quality Control for Gulick II Tape Measure

The Gulick II is a self-calibrating tape measure. No extra QC procedures are required.

14.2 VITAL SIGNS: BLOOD PRESSURE AND PULSE

14.2.1 Schedule of Administration

Seated blood pressure and heart rate measurement is performed during screening, at the Randomization Visit and at months 6, 12 and 18.

It is suggested that seated blood pressure and heart rate measurements be done at the beginning of a visit, after the participant has been sitting quietly for at least five minutes to allow blood pressure and heart rate to stabilize after movement or activity, such as walking.

During this five minute resting period, participants should NOT be engaging in any of the following: Reading, filling out forms, talking or crossing their legs.

14.2.2 Required Equipment, Materials and Personnel

Blood pressure will be measured with the Dinamap Monitor Pro 100 that is used for the Look AHEAD protocol. Cuff size will be determined by arm circumference. The participant's arm circumference should be measured with a tape measure to determine which of the following cuff sizes should be used: regular or adult, large arm, thigh and long arm.
Vital signs will be done following the Look AHEAD protocol. However, since this is not an outcome measurement in PRIDE, blood pressure and pulse will be recorded only once at each of the prescribed visits.

Printer Set-up:
Printer paper is loaded by pressing the notched (thumb print) indentation on the printer door to open. With the monitor turned on, place the roll of paper in front of the silver roller and the paper will automatically feed. As the paper touches the plates, it will begin to auto-feed into the printer. Once the paper begins feeding, slip the loose end through the slot in the door, close it and press the notched indentation to lock it.

The gray knob at the upper right of the monitor functions in a manner similar to a computer mouse. Rotate the knob to highlight options on the display. Push the knob to select a highlighted option (like "clicking" with the mouse.) It will be most advantageous to preset the printer with automatic printing as the default setting. This eliminates having to change the printer setting with each subject. To set the printer to this default, use the following steps:

1. With the monitor turned on, turn the gray knob to highlight MORE... and press. Next turn the gray knob to highlight SERVICE and press.
2. To enter Clinician Service Mode, a series of four code numbers must be entered. Highlight and press, in order, the numbers 1, 2,

3 and 4. Turn the gray knob to again highlight MORE... and press. Next turn to highlight PRINT and press. When the question appears RESTORE PRINT MODE ON POWER UP?, highlight YES and press.

3. Turn the monitor off, and then back on. Turn the gray knob to highlight PRINT and press. When AUTO/MAN is highlighted in the PRINT menu, press the gray knob to toggle between options until the option PRNT:AUTO appears on the lower right side of the screen. Return to the main menu by highlighting MAIN and pressing. The printer is now set for automatic printing.

The printed tape that comes out of the Dinamap should be kept in the participant's source document or clinic chart. The telephone number to order paper for the Dinamap is 1-800-558-5102.

14.2.3 Setting Initial Target Inflation

It has been recommended that we set the initial target inflation pressure as a permanent default at 180 mm Hg. The instructions are in the Dinamap manual but have been summarized as follows:

1. Select More… from the main menu
2. Select Service… from the next menu
3. Select the numbers 1, 2, 3, 4 sequentially to access the clinician service menu (page 57 in operations manual)
4. Select Press and adjust the target pressure to 180 mm Hg by turning the gray knob and press to set (page 58)
5. Select OK and press, then select Main

Remember that the target inflation pressure can be adjusted at anytime from the main menu by selecting Set BP and changing as desired. However, once the monitor is powered off the clinician service default of 180 mm Hg returns on power-up.

14.2.4 Procedures

Preparation: Ask the participant if there is any reason why you should not measure blood pressure using her right arm. (Mastectomy and illnesses involving the lymph nodes can affect which arm to use.) Then determine the participant's arm circumference, in order to select the appropriate cuff size for

the blood pressure measurement. This is done by the following steps (assuming the right arm is used, if not substitute left arm in the directions):

1. Ask the participant to bare the right arm and hold it at the side of the body with the elbow flexed to 90 degrees and palm up.
2. Measure the length of the arm from the acromion process (bony extremity that forms the highest point of the shoulder) to the olecranon process (tip of the elbow) and determine the halfway point in this length. Mark this midpoint on the posterior surface of the arm.
3. Have the participant relax the arm along the side of the body and place the measuring tape around the arm at the midpoint mark.
4. Holding the tape parallel to the floor, draw it around the arm with a degree of tension that keeps it snug against the skin, but without indentation of the flesh.
5. Measure the right arm circumference to the nearest tenth of a centimeter and record on the data form. Note that this measurement is not meant to be a precise anthropometric measurement, it is meant to determine appropriate cuff size only.
6. Using the arm circumference measurement, determine the correct cuff size according to the chart that follows:

Arm Circumference	Cuff Size
17-25 cm	Small Adult
23-33 cm	Adult
31-40 cm	Large Adult
38-50 cm	Thigh (or long arm, see text)

The sizes for cuffs are overlapping in order to have some flexibility in choice. The first choice for cuff should always be for the larger size. However, if the participant is small in stature, the smaller cuff size might be used to avoid having the cuff slide up over the shoulder or down the antecubital fossa.
If a participant's upper arm circumference would indicate use of the thigh cuff, but the arm is too short for the cuff, or the cuff does not remain secured when inflated, the long arm cuff should be used. This is often a problem with obese participants, resulting in readings that are too high or too low when compared to a manual measurement.

Taking the seated blood pressure and heart rate readings:

The subject should be seated with both feet flat on the floor and the right forearm resting on the table. Palpate the antecubital fossa and position the cuff around the arm so that the midpoint of the bladder length is at heart level, and the cuff arrow marked "artery" is aligned with the brachial artery. Cuffs are labeled with range and index lines. The correct cuff has been selected if the index line is within the range as the cuff is wrapped around the arm. The cuff should be wrapped snugly enough that no more than one finger-width distance exists between cuff and skin.

Have the participant rest for five minutes prior to taking the measurement. To begin the procedure, push the green and orange START/STOP button at the lower right corner. This will inflate the cuff and initiate the first reading. Once the reading is obtained, the data will appear on the screen, and the cuff will automatically deflate.

Tear the printout from the printer. Mark which arm was used and record the blood pressure reading on the VITAL SIGNS data form. Record the heart rate data from the first reading as the "Pulse" on the VITAL SIGNS data form.

If the cuff accidentally becomes inflated and it is not on a limb, it can be manually deflated by unscrewing the cuff from the cord and manually pressing the air out.

Note: *Monitor battery and screen life are optimized if the monitor is left plugged in, but is turned off at the ON/OFF button when the device will not be used for several hours, or until another day.*

14.2.5 Quality Control

All technicians performing the seated blood pressure and heart rate measurements on PRIDE participants must be certified according to Look AHEAD procedures and certification must be renewed annually.

APPENDIX 14A

STADIOMETER CALIBRATION LOG

1. Calibrate the stadiometer with a 600 mm rod once a month.
2. Record the measurement under "Trial 1".
3. If reading is not 600mm adjust the counter according to protocol and re-calibrate.
4. Record second measurement (if necessary) under "Trial 2".

Date	Trial 1	Trial 2	Staff ID#

APPENDIX 14B

SCALE CALIBRATION LOG

Scale Model & S/N:							
Date	**20 kg**	**Tech. Wt.**	**Tech + 20 kg**	**20 kg**	**Tech. Wt.**	**Tech + 20 kg**	**Initials/Comments**

CHAPTER 15

CONCURRENT MEDICATIONS

15.0 CONCURRENT MEDICATIONS

All medications that the participant takes regularly must be recorded during Screening (either at SV1 or SV2), and at months 6, 12 and 18. The participant will be asked to bring all her **prescription and non-prescription medications** to each of these visits and the Study Coordinator will enter each on the Medications Form. Either the trade name or the generic name should be entered, but not both.

15.1 MEDICATION DOCUMENTATION PROCEDURES

Remind the participant to bring all her prescription and non-prescription medications with her to either Screening Visit 1 or Screening Visit 2 and to the 6 month, 12 month and 18 month visits. Ask her to bring **only the medications that she takes on a regular basis**. For example, if she takes ibuprofen only occasionally she does not need to bring this. However, if she takes a baby aspirin every other day she should include the aspirin. It may be useful to place a reminder call to her the day before the scheduled appointment.

Examine the label on each of the containers that the participant brings to the visit. Mark the appropriate visit bubble and record either the trade name or the generic name starting in box number 1 on the MEDICATIONS FORM. If she takes more than seven medications routinely you will proceed to page 2 of the MEDICATIONS FORM.

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At each of the visits where concurrent medications are recorded, **you must document all of the medications the participant brings**, not just those that have been started since the last visit. If the participant forgets to bring her medications, you may schedule a telephone call with her to retrieve the information if, in your judgment, she will be able to give you reliable information by reading the medication labels to you.

Deleted: mentioned above the participant should bring to the clinic all of her regularly used medications

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15.2 EXCLUSIONARY MEDICATIONS

Use of the following medications at baseline excludes the participant from participating in PRIDE:

Brand Name	Generic Name
Steroids	
Azium	dexamethasone
Medrol	methyl prednisolone
	prednisolone
Deltasone	prednisone
	cortisone
Weight Loss Drugs	
Meridia	sibutramine
Xenical	orlistat
Diabetes Drugs	
Amaryl	glimepiride
DiaBeta, Micronase	glyburide
Glucotrol	glipizide
Glucovance	glyburide + metformin
Glynase	glyburide SR
Humalog, Novolog, NPH, Lente, Ultralente, Lantus, Humulin, Novolin, Novolog, or Humalog	insulin
Incontinence Drugs	
*Ascendin	amoxipine
Bentyl, Bentylol, Antispas	dicyclomine
Detrol or Detrol LA	tolterodine
Ditropan, Ditropan XL, Oxytrol patch	oxybutinin
Duloxetine	cymbalta
*Elavil, Endep	amitriptyline
Levsin, Levbid, Anaspaz, Urised, NuLev, Cystospaz, Prosed/DS	hyoscyamine
*Pamelor, Aventyl	nortryptyline
Pro-Banthine	probantheline
*Tofranil	imipramine
Urispas	favoxate

Deleted: Humalog, Novolog, NPH, Lente, Ultralente, Lantus, Humulin, Novolin, Novolog, or Humalog

Deleted: Insulin

*If the medications with an asterisk are prescribed for depression and not for incontinence, the participant may continue with the screening process.

If the participant starts taking any of these medications after she is randomized to PRIDE she will remain in the study, but will be noted as being in violation of the protocol.

The use of diuretics does not exclude a participant from PRIDE even though diuretics may affect urinary incontinence. It is expected that about the same number of participants in each of the randomly assigned groups will be taking diuretics.

CHAPTER 16

STUDY INTERVENTIONS

16.0 STUDY INTEVENTIONS

There are two arms in the PRIDE intervention program, a weight reduction program, called the Lifestyle & Behavioral Change Program, and the control condition, called the Structured Education Program. The weight reduction program combines diet modification and increased physical activity with a goal of sustained weight loss. The control condition emphasizes education and peer support.

A set of manuals have been developed by the PRIDE Interventions Committee and approved by the Steering Committee to ensure that both PRIDE sites implement the same intervention program in a uniform way. These include a participant manual for participants and an accompanying guide for counselors (see the lifestyle participant manual and counselor's manual available on the PRIDE website). Both sites will use these materials, which have been designed to be appropriate for individuals of different backgrounds and educational levels. In addition, two counseling staff from each site will be centrally trained by the Interventions Committee and monitored to ensure they deliver the intervention as designed. (Details of the lectures delivered during intervention training can be found in the Lifestyle & Behavioral Change Program Training Manual). These individuals will be responsible for training other staff members at their clinics who are to be involved in the intervention. Such training involves the following: (a) a review of the study protocol, (b) peer-tutored review of the lecture content presented during central training, (c) small group exercises similar to those offered during central training to practice therapeutic skills, (d) the trainee's observation of the senior interventionist conducting several group sessions, and (e) the senior interventionist observation of the trainee's delivery of several group sessions. All interventionists must receive certification for leading group sessions.

16.1 RANDOMIZATION

Women will be randomly allocated in a 2-to-1 ratio to either the weight reduction program (Lifestyle and Behavioral Change Program) or control condition (Structured Education Program). Randomization will be stratified by clinical center and is described in more detail in the Operations Manual, Chapter 12.1.

After 6 months of weight reduction intervention, women in the Lifestyle and Behavioral Change Program will be cluster randomized at each site by weight reduction counseling group to a skill-based or motivation-based weight maintenance program. Both 12-month maintenance programs will involve group meetings every two weeks. The programs will be matched on contact frequency and duration. The programs will differ in their

treatment focus. At entry into PRIDE, all participants will be provided with a participant handbook on incontinence education.

16.2 EDUCATION PROGRAM FOR CONTROL GROUP

Women randomized to the Structured Education Program will be invited to participate in hour long group educational sessions at months 1, 2, 3, and 4. At months 6, 9 and 15, the groups will meet again for group support sessions. The content of these education and support sessions will include information about weight loss, physical activity, healthy eating habits and general health promotion. The educational sessions will be delivered primarily in a group format, with individual make up sessions provided for participants who miss group sessions.

16.2.1 Goals For Structured Education Program

The ultimate goal of all Structured Education Program (SEP) sessions is retention.

Additional goals are as follows:

- Provide valuable learning experience
- Provide enjoyable experience
- Enhance bonding between participants of the SEP group and the Leader
- Provide an opportunity for group support

The Group Leader should identify him/herself as the Group Leader to each respective SEP group. Retention is served when group members are able to identify with one person who they associate as their leader. A bond will develop with the leader as the education sessions continue. The Group Leader should be a PRIDE staff member with a clinical background, such as a behaviorist, dietician, nurse, etc.

Resources for conducting the sessions for the SEP group may be found on the PRIDE website by clicking on the Structured Education Program link, then clicking on Session Documentation. It is critical to thoroughly read all the documents before conducting the SEP sessions.

16.3 SIX MONTH WEIGHT LOSS INTERVENTION

The weight loss induction intervention has been designed to provide a state of the art group-based behavioral obesity program that offers tailoring for individual needs by

incorporating flexibility with individual treatment strategies. The weight reduction program utilizes strategies that have been shown to be most effective for long-term weight loss and weight loss maintenance. These include a portion-controlled diet (i.e., a diet which provides portions of food with a fixed calorie and macronutrient content) during the initial phase of weight loss, a multi-component approach to intervention (including behavioral techniques, diet modification, physical activity, and social support), and ongoing regular contact throughout the follow-up period. Customization of the program to meet individual needs will be accomplished by encouraging individual participants to select the specific foods they wish to consume and the types of physical activities in which they would like to engage. Participants not adhering to the intervention will be helped to identify the barriers they are experiencing and to utilize the strategies that they feel will be most helpful to them in overcoming these barriers. The intervention will be delivered primarily in a group format, with individual make up sessions provided for participants who miss group sessions.

The Lifestyle & Behavioral Change Program is divided into two phases. Phase I is the weight loss phase that takes place from Months 1-6. During Months 1-6, participants are seen weekly for group sessions. Flexibility is provided to allow participants who miss a visit to attend an individual make up session. A total of 24 group intervention visits are scheduled during the first 26 weeks (six months). Phase II is a twelve month weight maintenance phase.

16.3.1 Intervention Counselors

A team of lifestyle counselors delivers the Lifestyle Intervention. The interventionists at each site will be individuals with expertise in nutrition, exercise physiology, and/or behavior modification. Experience providing weight reduction therapy and leading groups is an important qualification of all lifestyle counselors. It is important that each clinic provide office space for individual counseling contacts and a room that will accommodate group sessions for up to 15 participants.

16.3.2 Weight Loss Groups

It is anticipated that groups will be comprised of approximately 10 to 15 women. Thus, once participants are randomized, the maximum delay prior to the first group session should be 30 days. Group sessions are offered at different times of day and evening to accommodate different schedules; however, participants complete Phase I of the program with their assigned group (i.e., a closed-group

format that includes the same group members once the group starts and does not add new members).

16.3.3 Weight Loss Goals

The PRIDE Lifestyle & Behavioral Change Program is designed to induce a minimum weight loss of 7% of initial body weight during the first six months. Each clinical center is expected to achieve a mean weight loss of at least 7% across all their participants. Individual participants in PRIDE are encouraged to lose 10% (or more) of their initial body weight through the use of goal setting and other self-regulatory skills, with the expectation that "aiming high" will ensure a greater percentage of participants achieve the minimum 7% weight loss.

16.3.4 Diet

Restriction of caloric intake is the primary method of achieving weight loss. In order to aim for a weight loss of 10% of initial weight, the calorie goals are 1200-1500 kcal/day for individuals weighing 250 lbs or less at baseline and 1500-1800 kcal/day for individuals who weigh more than 250 lbs. These goals can be reduced to 1000-1200 kcal/day and 1200-1500 kcal/day, respectively, if participants do not lose weight satisfactorily. These calorie levels should promote a weight loss of approximately one to two lbs/week. The composition of the diet is structured to enhance glycemic control and to minimize cardiovascular disease risk factors. The recommended diet is based on guidelines of the ADA and National Cholesterol Education Program and includes a maximum of 30% of total calories from total fat, a maximum of 10% of total calories from saturated fat, and a minimum of 15% of total calories from protein.

During the first four months of the intervention (weeks 3-19), participants are encouraged to follow a portion-controlled diet, given findings that this approach produces significantly larger weight losses than having participants consume a self-selected diet of conventional foods. Portion-controlled diets provide servings of food with a fixed calorie and macronutrient content. Participants choose from two prototype diets. The first includes the use of a commercially available liquid meal replacement that replaces two meals and one or two snacks daily. This regimen is combined with an evening meal of either a frozen entrée or conventional table foods to provide a total of 1200-1800 kcal/day depending on the individual's baseline weight. The second option, for

those who do not accept or tolerate the liquid/prepared meal prototypes, involves the consumption of a structured meal plan, with the same calorie range, using foods that participants prepare themselves. Participants are provided menus that describe specific foods to be eaten for breakfast, lunch, dinner and snacks. Group sessions provide an opportunity to brainstorm strategies to incorporate these structured meals into daily lifestyle and problem solve difficulties that arise, as well as to tailor these diet options to the participant's preferences, lifestyle, and health status. Individuals who are successful and desire to continue on this diet are allowed to do so, and are reviewed monthly to re-assess their progress. Long-term replacement (with a liquid supplement) of one meal a day also will be an option, given the favorable long-term results reported by other investigators. Participants can choose to continue the one-a-day meal replacement plan for up to 18 months (i.e., until the end of Phase II). Participants will be provided with meal replacement products and/or coupons to obtain meal replacements at no cost to them.

16.3.5 Physical Activity

Physical activity is a cornerstone of the proposed intervention, because it contributes to long-term weight loss maintenance, improves cardiorespiratory and muscular fitness, and reduces risk factors for cardiovascular and metabolic disease. In addition, controlled trials employing physical activity as a key part of a weight loss intervention have observed significant reductions in the incidence of diabetes and hypertension.

The physical activity program of PRIDE relies heavily on unsupervised exercise, with gradual progression toward a goal of 175 minutes or more of moderate intensity physical activity per week by the end of the first six months. Specifically, participants are asked to walk 50 minutes per week during weeks 1-4, 75 minutes per week during weeks 5-8, 100 minutes per week during weeks 9-12, 125 minutes per week during weeks 13-16, 150 minutes per week during weeks 17-20, and 175 minutes per week during weeks 21-26. Exercise bouts of ten minutes and longer are counted toward this goal. Exercise is recommended to be spread over five days of the week. In general, occupational activity will not be counted towards the physical activity goal.

Moderate-intensity walking is encouraged as the primary type of physical activity. To enhance participation, the intervention will allow for individual choices in types of moderate physical activities and the tailoring of exercise programs based on each participant's physical fitness and safety issues.

Unsupervised exercise is encouraged for most sessions, as it has been shown to be as effective in weight loss and risk factor modification as supervised exercise, and appears to be more likely to be sustained.

16.3.6 Behavioral Strategies

Behavioral methods that have been demonstrated effective in producing and/or maintaining weight loss in previous studies of overweight populations will be integrated into all intervention sessions. Self-monitoring is a cornerstone of behavioral interventions and will be encouraged throughout the intervention. Participants will be asked to self-monitor dietary intake (foods eaten, portion size, calorie content, and fat grams) and physical activity (including type, duration, and number of steps walked, when applicable) in a seven-day diary that will be provided to them. Diaries will be collected and reviewed by intervention staff and returned with specific, written feedback. Participants will be taught to review the diaries to learn about their diet and exercise habits, to identify specific targets for behavior change and to establish realistic behavioral goals. Self-monitoring review will emphasize use of diary data as feedback to reinforce incremental progress toward specific behavioral goals. Participants will be instructed in strategies for setting short and long term goals and for monitoring progress toward these goals. Frequency of self-monitoring will taper as the intervention progresses, however, resumption of more frequent use of this strategy will be encouraged during high risk periods, as well as when participants begin to regain weight.

Other behavioral strategies will be included. Problem solving techniques will be introduced and reinforced throughout the program to resolve barriers to behavior change. Participants will also be instructed in stimulus control strategies to alter their environments to decrease the salience of cues to eating high-calorie, high-fat foods and cues that trigger inactivity, as well as to increase the salience of cues that encourage increased physical activity and appropriate low-calorie eating patterns. Relapse prevention training will be included to increase skills at identifying and coping with high risk situations and dealing with lapses so that they do not lead to eventual relapse.

16.3.7 Resources for Intervention

There are additional resources in addition to the Operations Manual that delineate very clearly the content of the lifestyle treatment that is to be delivered to each participant (Participants' Manual) and suggestions on how to deliver

each intervention session (Counselors' Manual). The Counselors' Manual also contains a section that describes the content of the intervention training for PRIDE. Interventionist training includes discussion of the following topics: (1) dietary issues, (2) how to prescribe physical activity, (3) how to lead effective groups, (4) tailoring treatments, (5) handling difficult participants, (6) managing participants with rapid and excessive weight loss, and (7) managing long-term adherence to treatment.

16.3.8 Quality Control: Maintaining the Fidelity of the Intervention

Central training and review sessions will be provided for intervention staff on an annual basis. These training/review sessions will contribute significantly to the quality of data by providing an opportunity for learning/updating intervention and data collection skills, recruiting skills, addressing specific problems related to adherence, and promoting study camaraderie. Since the need for replacement training is difficult to predict, the scheduling of these sessions will be done on an *ad hoc* basis. In addition, the interventionists from both sites meet weekly, or as necessary, by telephone to discuss the structure and implementation of the intervention sessions.

16.4 MAINTENANCE PHASE

At the completion of Phase I, the weight loss intervention groups will be cluster randomized to a Skills Based Maintenance Program or a Motivation Based Maintenance Program for Phase II: Months 7-18. During Phase II, participants in both maintenance programs will attend group sessions every two weeks, although a few individual sessions will be offered at selected points in the maintenance program (replacing the group session). Both maintenance programs will have individual sessions at the same point in the maintenance program, although different content will be offered to the two conditions. Intervention sessions for each maintenance program are outlined in detail in the intervention manual (counselor manual). (Please see Lifestyle and Behavior Change Program Manual)

CHAPTER 17

SERIOUS ADVERSE EVENTS/PROCEDURES

17.0 SERIOUS ADVERSE EVENTS/PROCEDURES

17.1 DEFINITION

A serious adverse event (SAE) is defined as any adverse experience, occurring to a PRIDE participant during the course of the study that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require inpatient hospitalization may be considered a serious experience when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Any overnight hospital stay is an SAE.

In addition to the Serious Adverse Events described above, we would like to document *outpatient* procedures or surgeries pertaining to the abdomen or pelvic region. Please use the Serious Adverse Events form to document procedures such as the following:

- Bladder suspension through an incision in the vagina (tension-free vaginal tape {TVT} or trans-obturator tape {TOT})
- Laparoscopic bladder suspension (laparoscopic Burch)
- Laparoscopy for pelvic surgery (involving ovary, fallopian tubes, uterus including hysterectomy, etc.)
- Laparoscopy for abdominal surgery (gall bladder)
- Cystoscopy (examination of interior of bladder)
- Hysteroscopy (examination of interior of uterus) and /or D & C
- Repair of vaginal prolapse (anterior colporrhophy or cystocele repair, sacrospinous ligament suspension and/or urethral plication or Kelly plication)

Events that occur during screening need not be reported to the Coordinating Center. Only events that occur between the date of randomization and the date of the final visit should be documented.

17.2 REPORTING SERIOUS ADVERSE EVENTS (SAEs)

17.2.1 Lag Time to Report

The Investigator must notify the Coordinating Center as soon as possible by telephone if any serious or unexpected adverse event occurs in any participant *after the participant has been randomized*. The SERIOUS ADVERSE EVENT FORM should be completed and faxed to the Coordinating Center the same week that the event is reported.

All such reportable events must be monitored until the condition subsides and/or the cause is identified. Updates to the SAE form can be made, if new information becomes available, by posting a query to the website and then making an addition or change to the form.

17.2.2 Records Requested

Surgical reports and discharge summaries for pelvic and abdominal procedures performed in the hospital should be requested. All other SAEs will be self-reported. Any records obtained by the site in order to complete the SAE data form should be filed in the participant's chart at the site. Do not send copies of hospital records to the Coordinating Center unless specifically requested.

17.2.3 Reporting Responsibilities

The Coordinating Center is responsible for notifying both the sponsor (NIDDK) and the Data and Safety Monitoring Board of all serious adverse events. The Principal Investigator is responsible for notifying the site's local IRB according to institutional guidelines.

17.2.4 Filling Out the SAE Form

Complete the banner information and enter the date of the visit if the participant is reporting the event in person. Alternately, enter the date you receive enough information about the event to warrant a report. Choose the visit bubble that is closest to the date of the event.

Please work through the form carefully and enter as much information and as many dates as you are able. Note that question 1 can have multiple responses.

If the participant has had an *outpatient* procedure pertaining to the abdomen or pelvic region, mark the bubble for hospitalization and enter the date of

the procedure in **both** the "Date hospitalized" and the "Date discharged" boxes.

Question 3: Enter the diagnosis. Remember to use all capitals, be brief and try to obtain the correct medical diagnosis. If no diagnosis is available enter the main symptom experienced by the participant. If appropriate, include the cause of the event (e.g. "Hysterectomy due to excessive vaginal bleeding"). The terms you enter for "Diagnosis" will be reproduced verbatim on data listings and reports so please be precise and concise.

Question 4: Choose the one response that best describes the participant's condition at the time you are filing this report. If the outcome does not fall into any of the categories provided, mark "Other" and enter a very brief description of outcome. Do not write outside the boxes because the data will not be accepted to the database.

Question 5: Please indicate whether or not the participant will continue in the study. If the participant will no longer continue to be followed, please fill out a Termination Report.

Question 6: Treatment administered: please mark all that apply.

Question 7: Is event related to the intervention? Please choose one response only.

Question 8. Use these boxes to provide additional helpful information. Again, please be brief, one letter per box, all capitals, don't write beyond the boxes.

It can be difficult to describe life events on a form! Please call the Coordinating Center if you are uncertain about completing any parts of this form.

CHAPTER 18

DATA SYSTEM AND MANAGEMENT

18.0 DATA SYSTEM AND DATA MANAGEMENT

18.1 PURPOSE OF DATA MANAGEMENT SYSTEM

The purpose of the University of California, San Francisco (UCSF) Data Management System is to provide high quality data and study management tools in a timely fashion to the study investigators. Machine-readable forms and internet technology are utilized to provide data access and editing.

18.2 DATA SYSTEM OVERVIEW

The PRIDE data system consists of three related components: DATA INPUT, DATA QUERYING, and QUERY RESOLUTION.

The DATA INPUT component starts with data collection forms that are filled out at the clinical site and sent to the UCSF Data Management Group (DMG) via a standard fax machine. The images of the forms are stored in an image-management system. The DMG does not receive any paper in the data acquisition process. An operator at the DMG will verify the forms by manually viewing the image on a monitor—an important step that filters many misinterpretations in the automated data input. Verified data are then sent to a database. Reports on the study website provide feedback on the data input process.

The second component is DATA QUERYING (also known as the query or edit report). This is an error-checking program that is run each night against the entire database. The results of this process are made available on the study website. The website is also the means for study staff to post their own queries to correct errors they discover after faxing forms to the DMG.

The third component is QUERY RESOLUTION. Using the "edit report" (query list) on the website, study staff can change the data in the study database to correct errors or inconsistencies in the data. An electronic audit trail is created whenever data is changed.

18.3 ACCESSING THE WEBSITE

18.3.1 User Name and Password

To print study forms and view or update study data, you will need to access the PRIDE website. To do this you need a unique User Name and password.

If you have not received this information, please notify your study coordinator. Study coordinators should contact the Project Assistant at the Coordinating Center to request User Names, access levels, and Passwords for new clinic data users and to report access problems.

Your User Name is composed of the first initial of your first name, followed by your last name (do not include any spaces between your initial and your last name).

For example: Josephine Schmoe
User name: JSchmoe

Access levels affect what features of the website the user is able to access. The different levels are based on the ability to view or to change participant data. The chart below describes the different levels. For example, the clinic data user who will be fixing problems with the forms should have the highest level access (PRIDE_PptData_F). Staff who deliver the weight loss intervention should have the lowest level of access (PRIDE_PPtData_W).

Access Level		User Role Description
PRIDE_PPtData_W	1	users can access all the website features except participant data
PRIDE_PPtData_R	2	users can access all the website features and view data
PRIDE_PPtData_F	3	users can access all the website features, view data, and change data (for their site only)

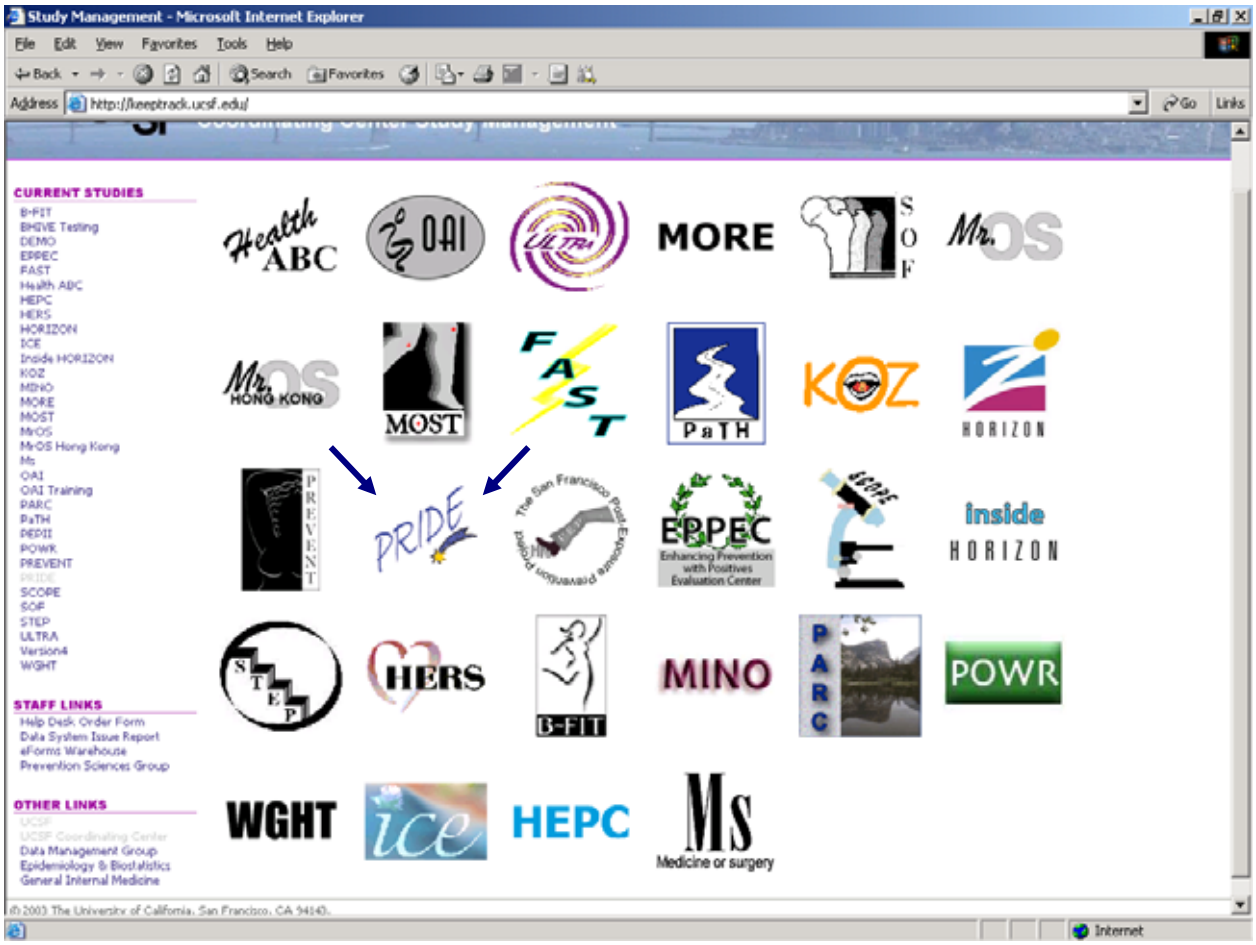
18.3.2 Navigating the PRIDE website

*Please note that the PRIDE website works optimally when used with Microsoft Internet Explorer version 5.5 or higher.

Once the browser is selected on your computer, the following URL (web address) should be entered:

http://keeptrack.ucsf.edu

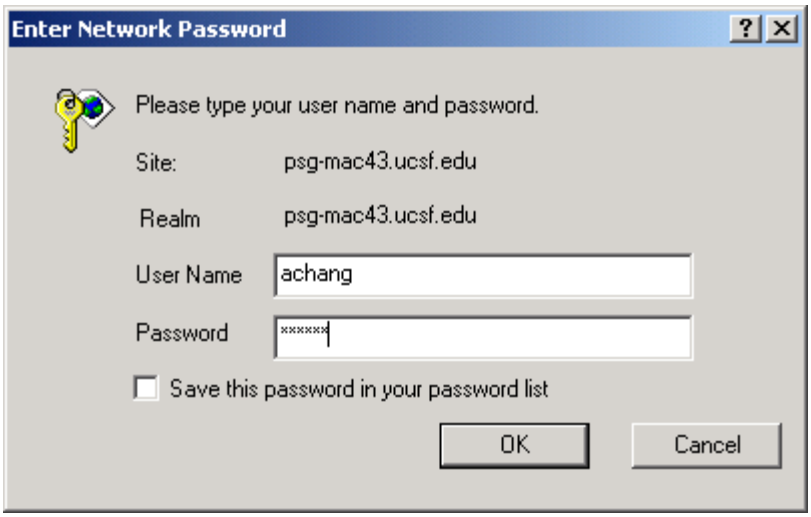
The UCSF Coordinating Center Study Management homepage is then displayed, which contains numerous study logos, displayed below. Please click on the PRIDE study logo.



A box will pop up (see below), asking for your Network Password. You must now enter your User Name and Password. If you haven't been assigned a user name and password please notify your Site Coordinator who will contact the Project Assistant at the Coordinating Center.

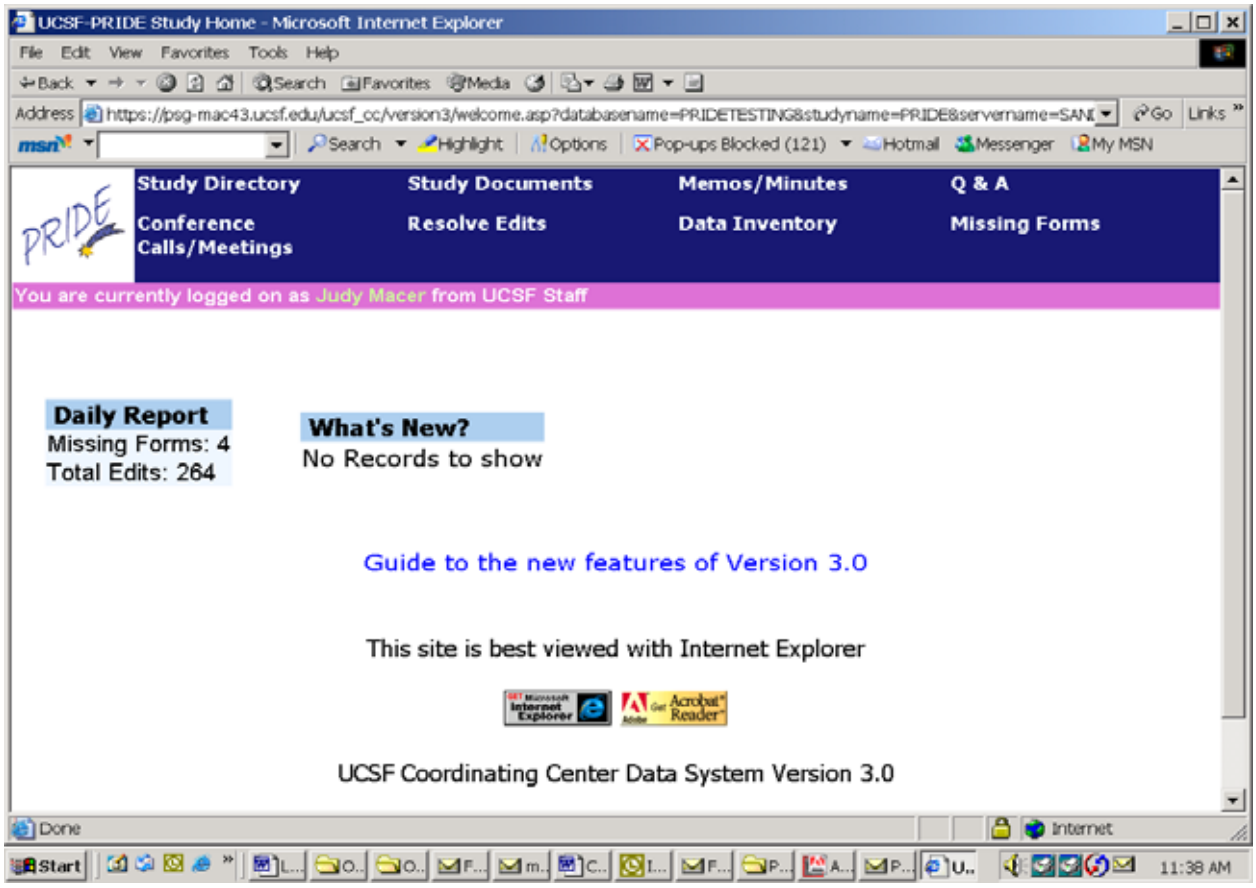
Login

This screen prompts the user to enter username and password in the appropriate fields. Once a valid username and password combination has been entered and verified, the user can click on the "OK" button below those fields and proceed to the study homepage.



If you type in your information incorrectly, you will be prompted to try again. If you attempt to log-on three times without success, your account will be locked by the system. After the third failed attempt, you must wait 2 hours before you may try to log on again. Therefore, please be careful when logging-in and be sure that you do not have the Caps Lock on.

Next, you receive a welcome message (see below) giving your name and affiliation (study site or other institution). This password-protected WWW site is the study's data collection and management hub.



18.4 FEATURES OF THE WEBSITE

The PRIDE website includes both administrative and data viewing and editing components. These include:

Administrative Features

Conference Calls/Meetings
- The Conference Calls/Meetings page shows all scheduled future conference calls and meetings. Using the drop-down menu, select the item of interest to view the current calendar.

Study Directory
- The PRIDE Directory contains contact information for PRIDE Investigators and staff.

Memos
- All PRIDE study memos will be available through Outlook – see the section on Memo Archive

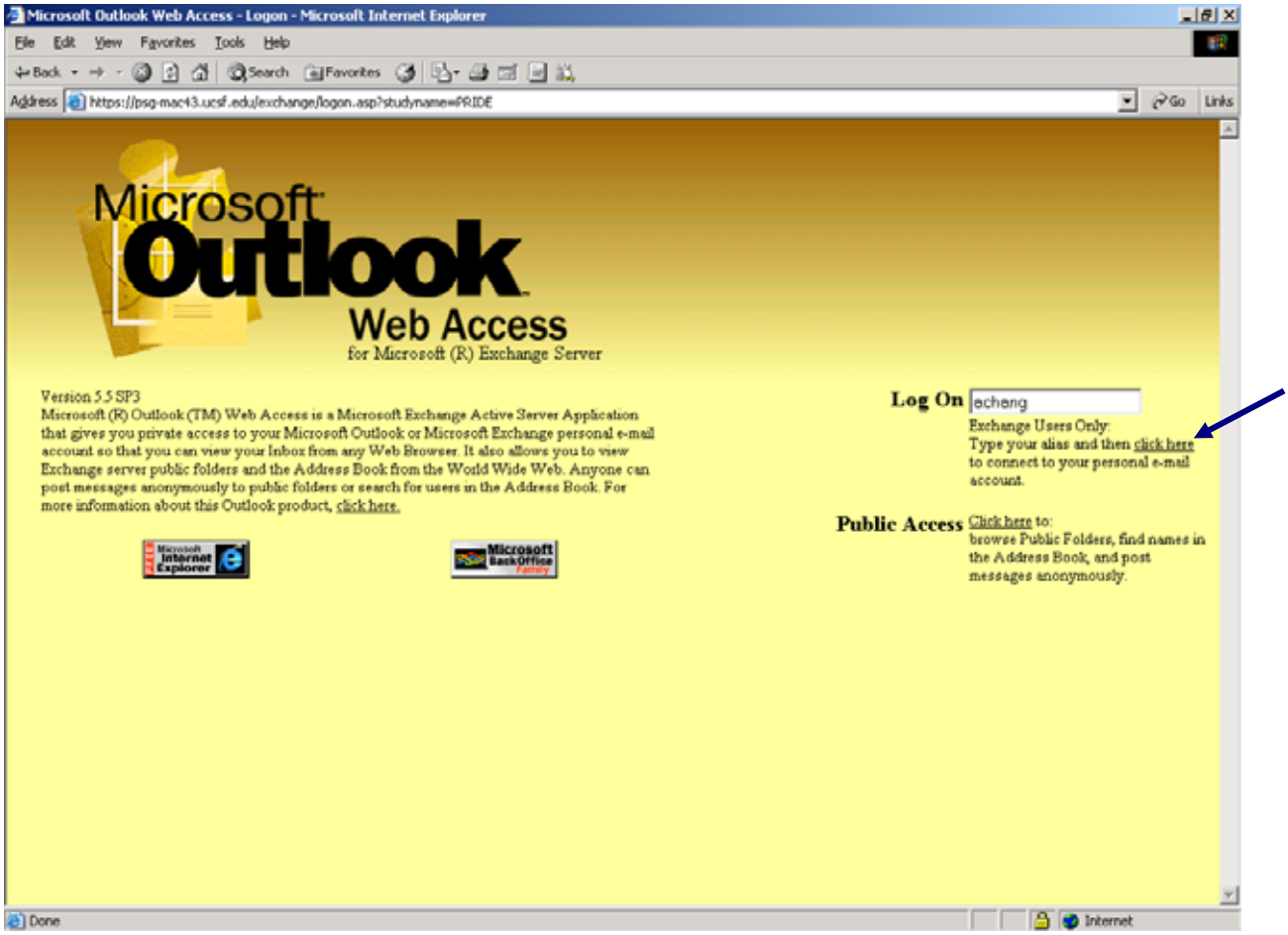
Questions & Answers	PRIDE study questions (e.g., questions about study procedures, inclusion/exclusion, addressing queries, etc.) can be submitted through the PRIDE Q&A Form on the website. **Answers will also be posted at this site.**
Reports	• Reports on recruitment and visit compliance will be available
Study Documents	• Downloadable pdfs of all study forms, manuals and instructions are available at this site. Instructions for downloading forms and documents are given later in this chapter.

Data Features

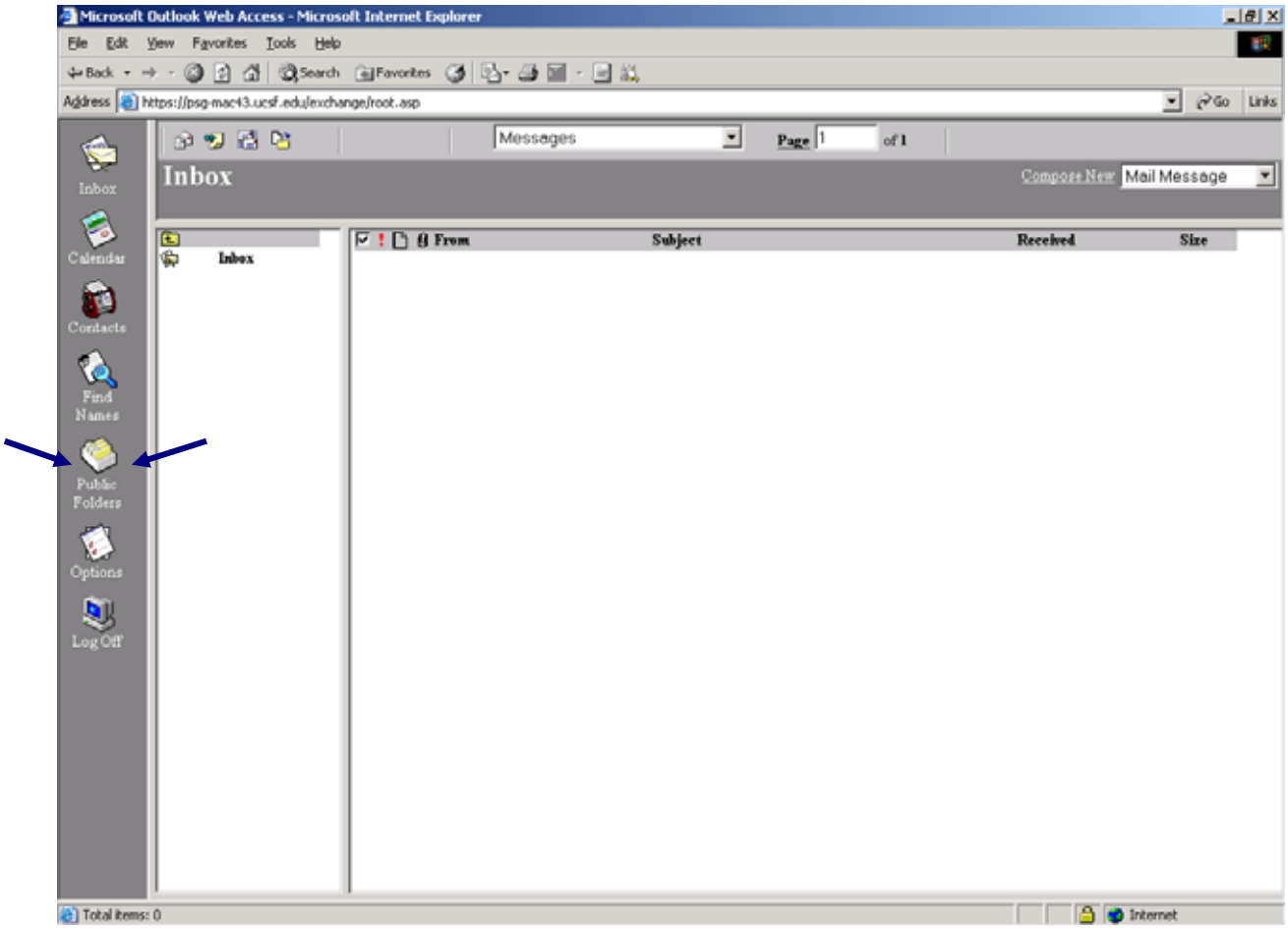
Data Inventory	• All forms, listed by participant can be viewed as html or pdf.
Missing Forms	• Display of forms that are expected but missing from visit packets.
Rejected Forms	• Display of forms that have been rejected by the system because they are duplicate forms, contain an incorrect Subject ID #, or missing visit bubble.
Resolve Queries	• This feature allows study staff to address queries that have been generated by the system. Queries typically require information on fields that are out of range, missing, or inconsistent.
Post Queries	• If the site discovers that an error was made on a form, a query can be generated and addressed by site personnel. This corrects the database and leaves an audit trail.
Audit Trail	• Displays the history of all queries addressed, the original data in the field, the date the change was made, the person responsible for changing the data and the reason for the change.
Audit Trail Summary	• Provides a summary of all changes made to a form or variable.

18.4.1 PRIDE Memo Archive

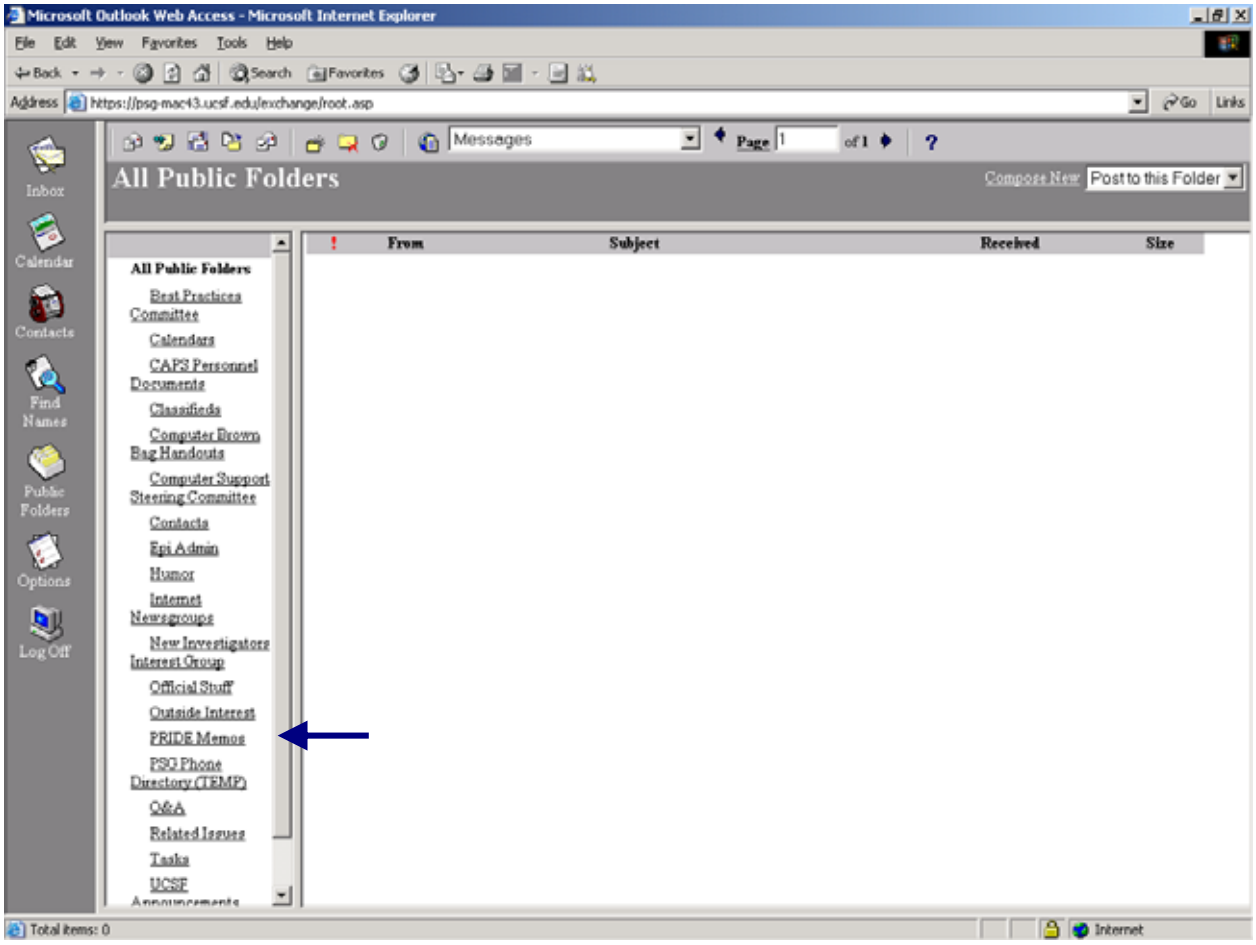
From the PRIDE homepage, click on Memos/Minutes and you will be sent to the Microsoft Outlook Webpage. PRIDE memos are archived in the UCSF Prevention Sciences Group Microsoft Outlook Server. Your Logon ID will be your username (ie achang). Please type in your ID and press the enter key (or click on "click here").



Please click on “Public Folders”.

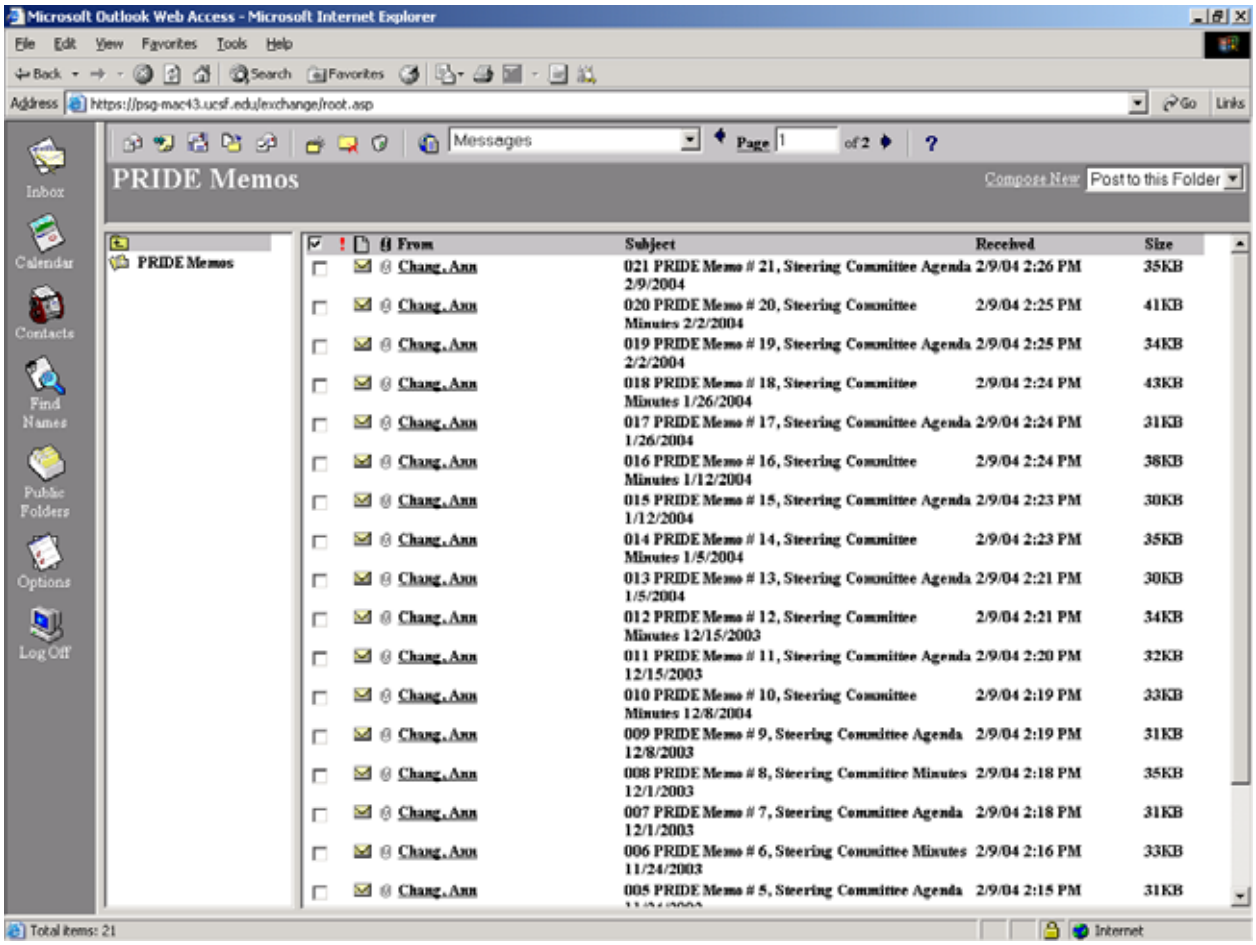


Then click on PRIDE Memos.



You will not be allowed access to other selections on this page.

Memos are displayed.



18.4.2 PRIDE Question and Answer (Q&A)

The Q & A site posts the answers to questions regarding any aspect of the study. Questions and answers are posted to make sure that all study staff receive the same answer to a specific question. The answers to questions will be periodically incorporated into revisions of the PRIDE Operations Manual.

To Submit a Question: To access the Q&A form, click on the Question & Answer Icon in the banner located at the top of the PRIDE web pages and then click on the "Ask a Question" link. Please use a separate form for each question and be as detailed and clear as possible. If applicable, send supporting documentation or examples, or refer to specific forms or sections of the PRIDE Operations Manual. Please complete the form on the web and press

the "Submit" button ONCE. This will email the form to the Project Assistant at the Coordinating Center, who will triage the question(s) to the appropriate person(s) who can answer it. Answers to your questions will be posted on the website. Discussing questions with Coordinating Center staff before posting them to the web site often clarifies the question.

Viewing Previous Questions & Answers: The answers to questions submitted to the Coordinating Center will be posted on the website by date and topic category. This listing will be available for viewing by anyone who has access to the site. The questions and answers can also be searched for specific terms.

The "Data Features" of the data system, available on the website are discussed further in the following sections.

18.5 CLINIC PROCEDURE

Clinical site personnel should check the website daily to confirm that the DMG has received all of the forms faxed the previous day, to address queries that may be posted, and to check for rejected and missing forms. The list below is an overview of clinic procedure for each participant:

1. Review and fax forms
2. Complete fax log (see Chapter 5, Appendix 5C) after you do the following:
   a. Check for fax confirmation
   b. Check **Missing Forms** report
   c. Check **Rejected Forms** report
   d. Check **Data Inventory** to ensure data received by DMG
3. Check edit report by going to **Resolved Queries**
4. Address all queries

18.5.1 Receipt of Faxed Forms in the Data System

Completed data forms should be reviewed and faxed to the DMG (**415-597-9174)** at the end of each day. The DMG data system will not receive any paper copies of the data forms. The data coordinator at the site should document on the Fax Log that the fax transmission was successful. While the normal fax confirmation might ensure that the data server has received the image, there are other ways in which data is prevented from proceeding to the study database. For example, a data form is sometimes not readable by the system because pages stick together when fed through the fax machine or the form identifier box in the lower right-hand or upper left-hand corner of the form is damaged. In these cases, the data form may need to be re-faxed. If this occurs, the DMG data verifier will inform the respective site via phone, e-mail, or via the **Rejected Forms** or **Missing Forms** report on the website.

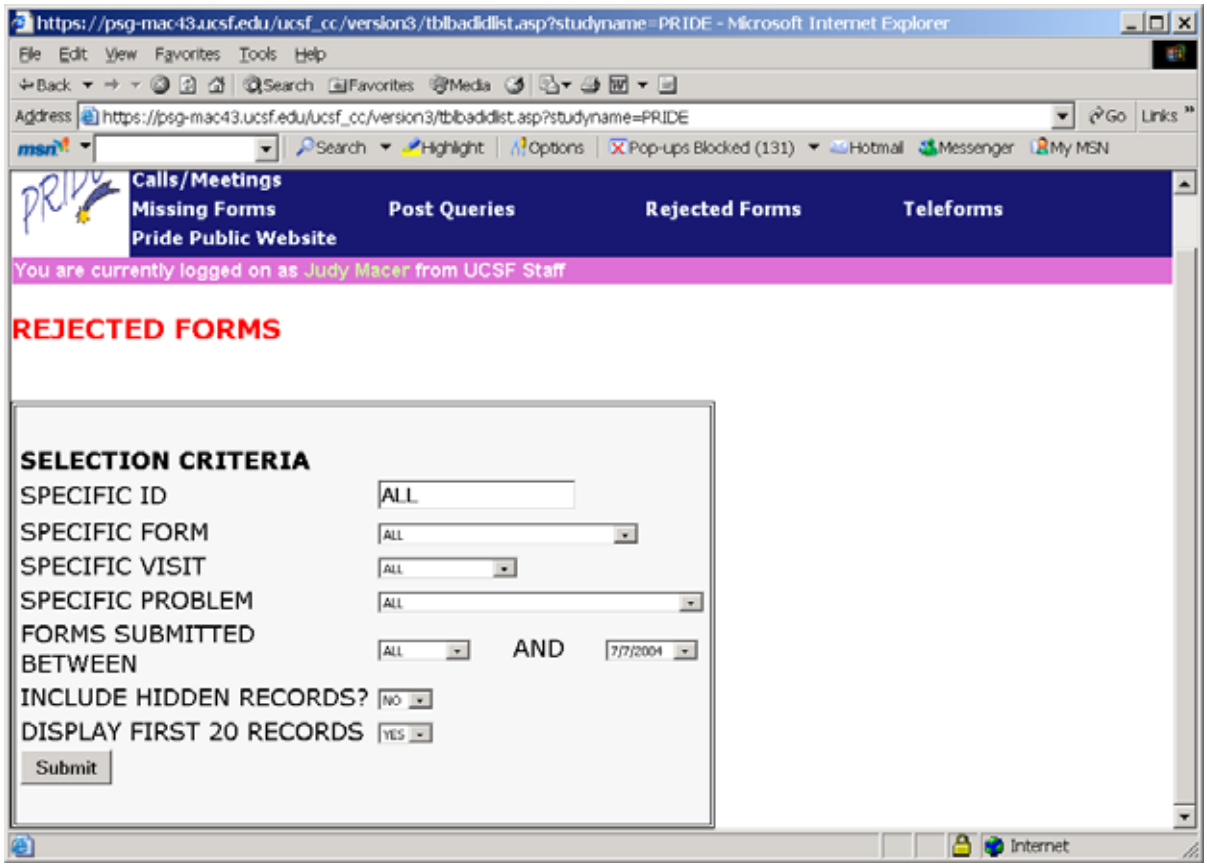
Once the data system has "evaluated" the data form, it is 'verified' by an operator (verifier). During the verification process, a DMG operator does an on-screen inspection of all questionable aspects of the faxed form. Once the form has been successfully verified, it will be available for viewing and editing on the study website.

The DMG will attempt to verify all data the same day that it is received; however, this may not always be possible. Once verified, the form should be listed in either the **Data Inventory** report on the study website (if no major problems were noted) or in the **Rejected Forms** or **Missing Forms** (if there were significant problems). The day after a form has been faxed to UCSF, the site data coordinator should verify that the form has been processed by reviewing the **Data Inventory** report on the study website. If a form is not present, an e-mail message should be sent to the CC Project Assistant, listing the Subject ID #, Acrostic, form, and date sent. Data staff at the DMG will resolve the discrepancy and report back to the clinical site within 24 hours.

18.6 FORM RECEIPT PROBLEMS

18.6.1 Rejected Forms

Even when a form is successfully processed by the verifier, information from it may not be added to the database. All such forms will be listed in the **Rejected Forms** report on the website, along with the reason for rejection. Specific selection criteria can be chosen when viewing **Rejected Forms**. By choosing "select all" the program displays all rejected forms, along with the reasons the forms were rejected. Rejected forms have NOT been entered into the database. The Rejected Forms Report is updated nightly.



There are 3 reasons why forms are rejected:

Problem #1: ***Subject ID # does not match Gold Standard ID***
Explanation: There isn't an Eligibility Screening Form in the system with the Subject ID # on the rejected form. This can occur if the Eligibility Screening Form has not yet been faxed or the Subject ID # on the rejected form is

incorrect.
Action: If the Subject ID # on the rejected form is incorrect, the correction should be made and the form should be re-faxed. If the Subject ID # is correct, the Eligibility Screening Form has not yet been received. The Eligibility Screening Form should be faxed along with the rejected form.

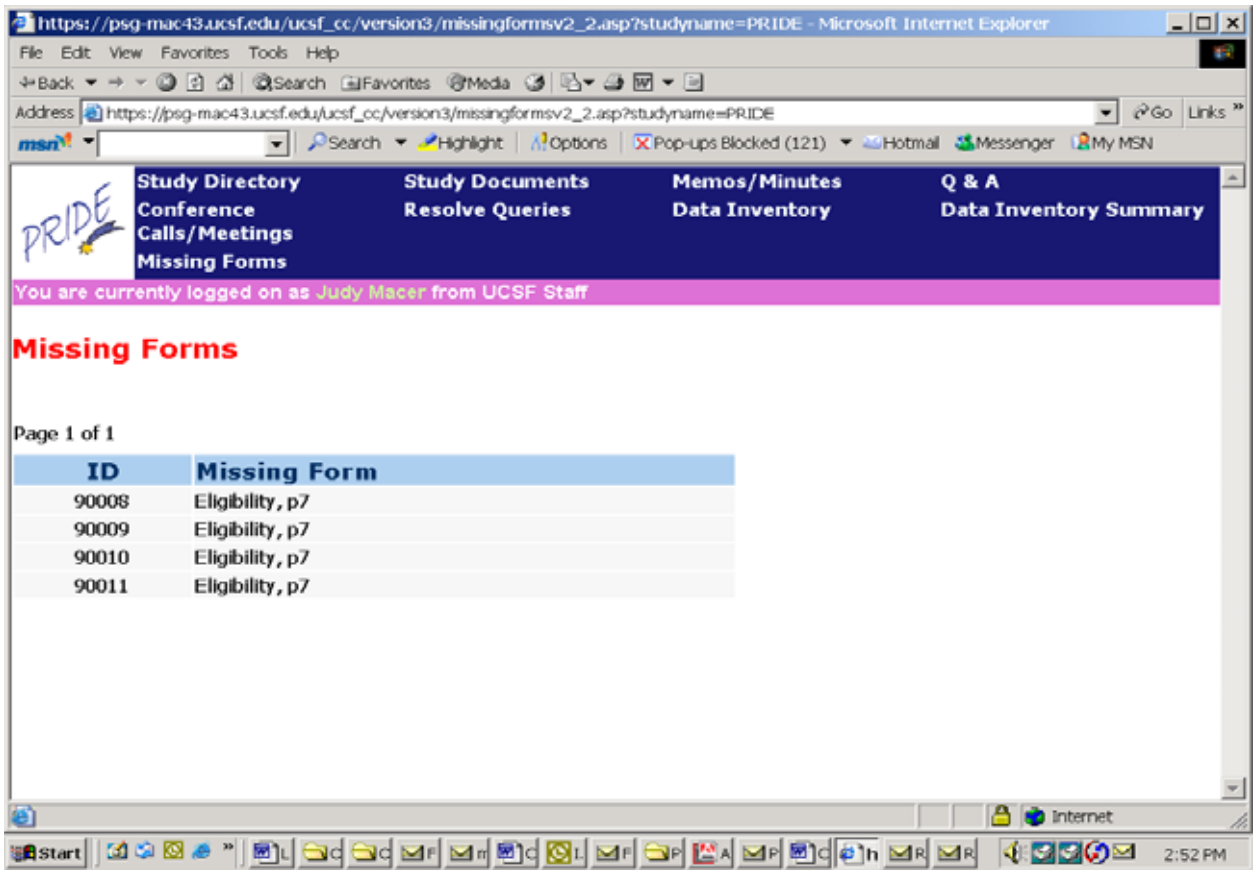
Problem #2: ***Acrostic does not match***
Explanation: The Acrostic was not filled out or was incorrectly filled out.
Action: Check the Acrostic; missing data should be filled in, an incorrect Acrostic should be corrected, and the form should be re-faxed.

Problem #3: ***Primary keys match form already in table***
Explanation: A duplicate form, with the identical Subject ID #, Acrostic, and other unique information is already in the database.
Action: Check **Data Inventory** to view the form already in the system. If the form in the database is NOT an exact duplicate of the form you are trying to fax, check to make sure that all identifying information is correct on BOTH forms: Subject ID #, Acrostic, Visit Date, and Staff ID #. If an error is found on the form you are trying to send, correct the error and re-fax. If an error is found on the form already in the system, contact the CC Project Assistant. Corrections to unique identifiers cannot be made through the query system.

NOTE: Once the reason that the form was rejected has been resolved, the form must be removed from the Rejected Forms Report. "Hide" should be clicked following the resolution to any problem in the **Rejected Forms** report.

18.6.2 Missing Forms

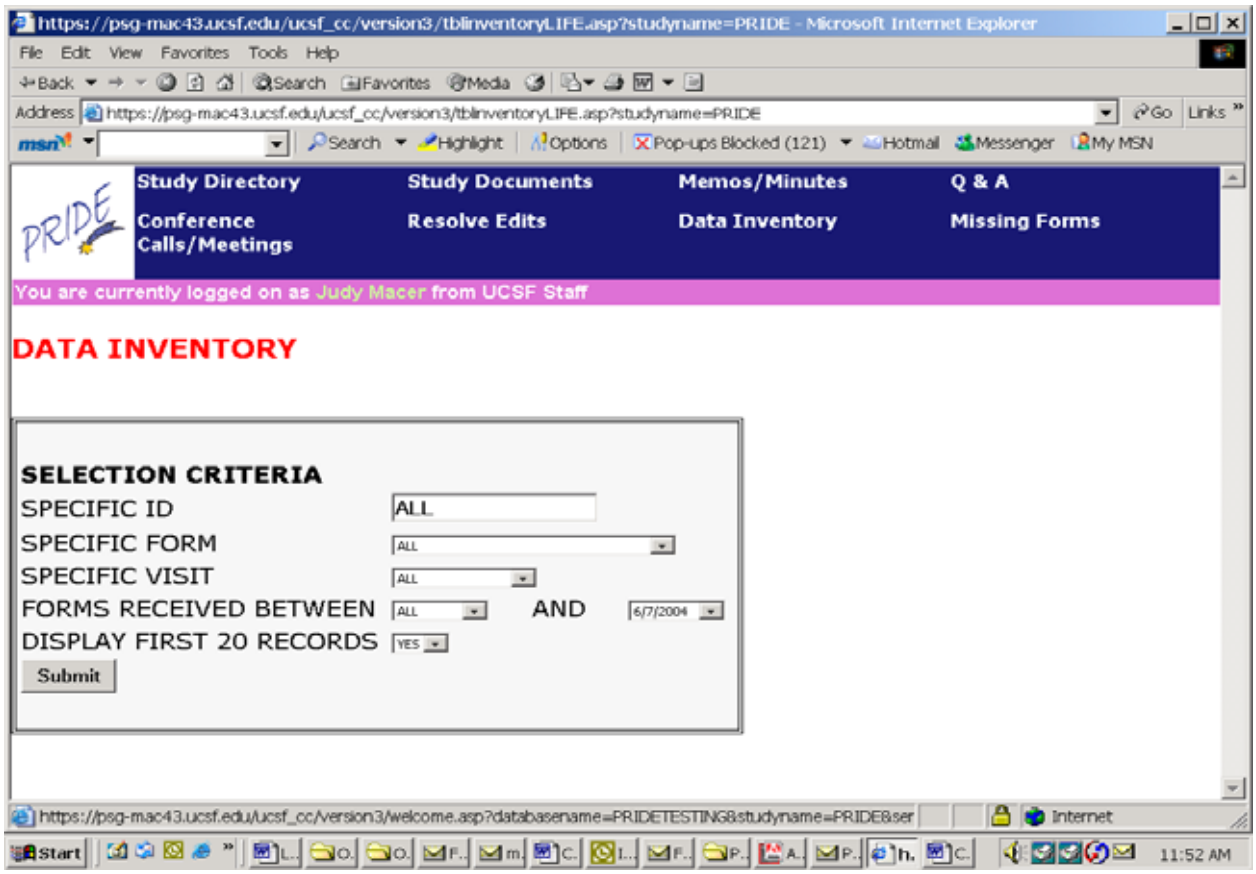
The **Missing Forms** report lists all participants for whom one or more forms, from any given visit, are missing. Although clinics fax entire visit packets, some forms may not be received by the DMG data system. This could occur, for example, if forms stuck together when being fed into the fax machine or were inadvertently left out of the faxed packet. Forms that appear on this report should be re-faxed immediately. When the form is successfully re-faxed, it will disappear from the **Missing Forms** report.



18.7 DATA INVENTORY

Once the information from the data forms is accepted into the database, the study data are available for viewing in the Data Inventory. This is a report of all completed forms received by the DMG database from your clinic and is a way to confirm that a form has been successfully received and processed at the DMG. The inventory is updated immediately after a form is verified.

Data cannot be changed or updated in Data Inventory, only viewed. The image below shows the website screen, prior to specific selection criteria being selected for Data Inventory.

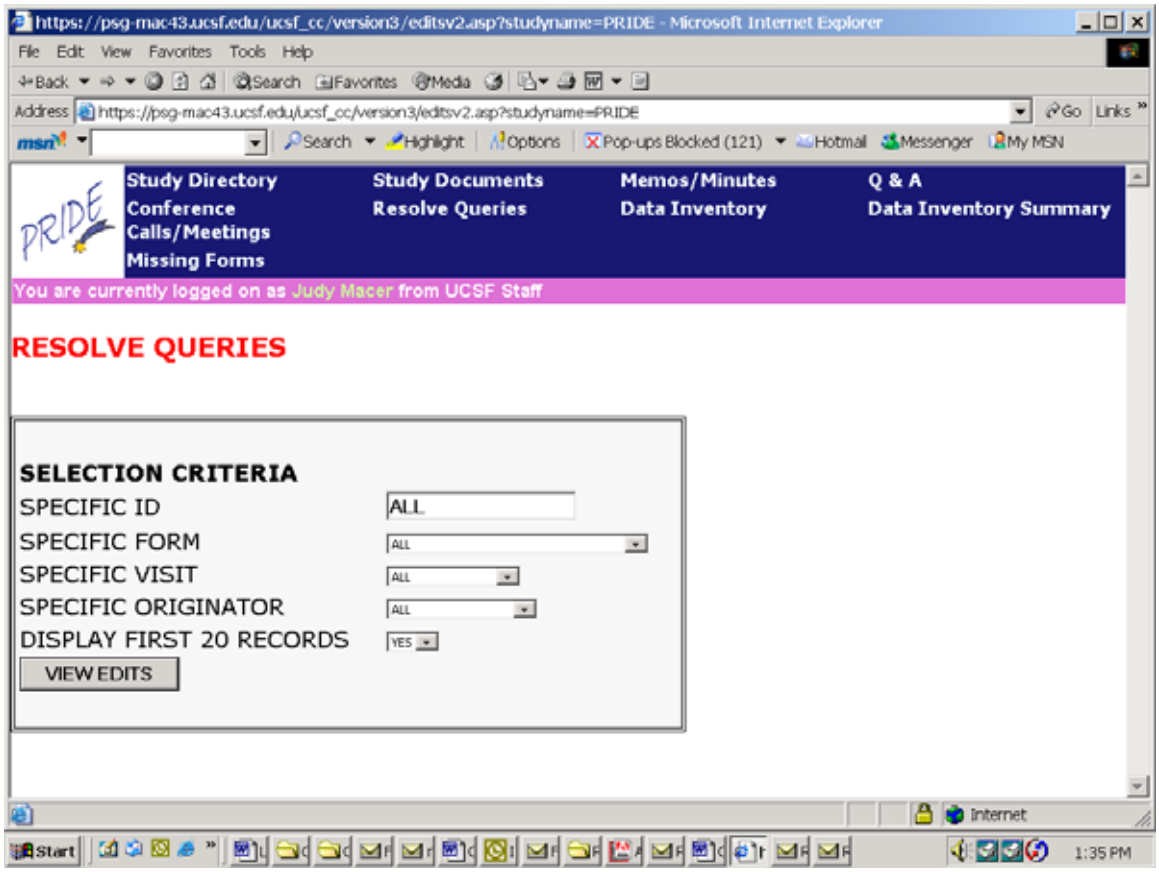


After selection criteria have been chosen, click on the "Submit" button. The forms that match criteria are then displayed.

Data on each form may be viewed as either an html or pdf file (pdf looks the way the forms have been printed); view type may be selected from the view menu.

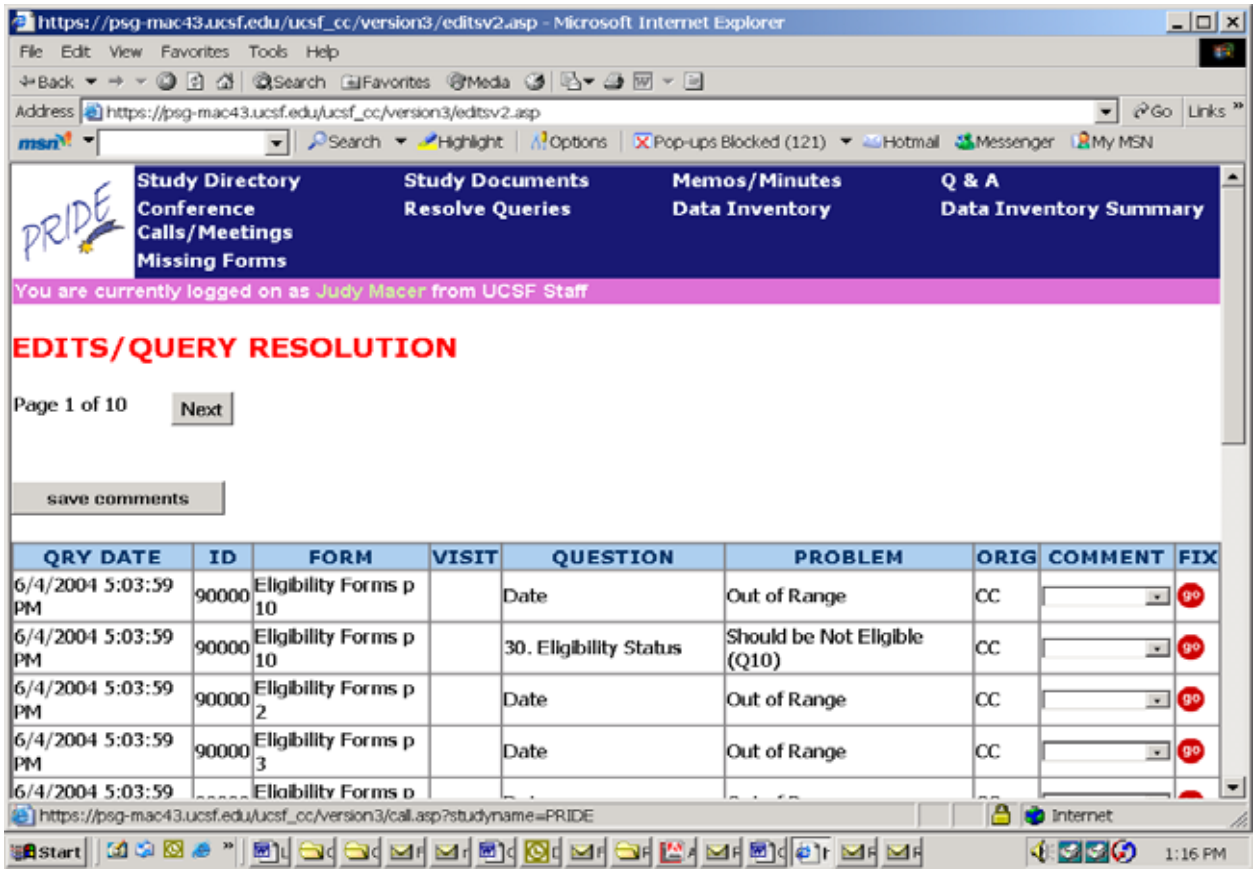
18.8 DATA QUERIES

Each night, all of the study data undergo a set of error-checking programs. The programs include checks for missing data, adherence to the skip patterns on a form, data consistency, and unusual outlier values. Access the queries by clicking "**Resolve Queries**" on the website.



18.8.1 Viewing Queries

View the queries for your site by selecting specific criteria and then clicking "VIEW EDITS". We recommend that you use the default option "ALL" in each of the selection criteria to keep the database as up to date and accurate as possible. Queries should be resolved on a daily basis.



The three most common types of queries are described below:

Error type

Missing — **Problem:** A required question shows no data.
Resolution: The correct answer to the question should be added or it should be confirmed that the answer to the question cannot be obtained.

Out of range — **Problem:** The value for the data is not within the allowable range. For instance, a date of 1/2/2341 would be noted as

out of range.
Resolution: The correct value should be entered or the unusual value should be confirmed as correct.

Inconsistent **Problem:** The question has been answered, but should not have been answered or is incorrectly answered, based on a response to an earlier question. The answer is logically inconsistent with the answer to an earlier question.
Resolution: The answer to this question should be deleted orchanged, or the answer to the earlier question should be changed.

IMPORTANT: All data on the website and the hard copy data forms should be consistent. If data are changed on the website, the appropriate changes ***should be made on the data form, accompanied by initials of the person making the change, the date the change was made and the reason for the change***. Likewise, if changes are made on the data form after it is faxed into the data system, the ***data already in the system must be edited using the query system***.

18.8.2 Resolving Queries

Sites are expected to address all queries directly on the website. There are two ways to address the queries: 1) make a change to the database by using the "Go" button in the "FIX" column or 2) enter text in the "comment" section. Most queries should be resolved with a data change. "Comments" are usually a last resort.

As with the **Data Inventory** report, the list of queries can be limited to a specific Subject ID # or a particular form. Most of the time, you will want to view and address the complete query report. By keeping up with the edits as they appear, you can keep the length of this report short and manageable.

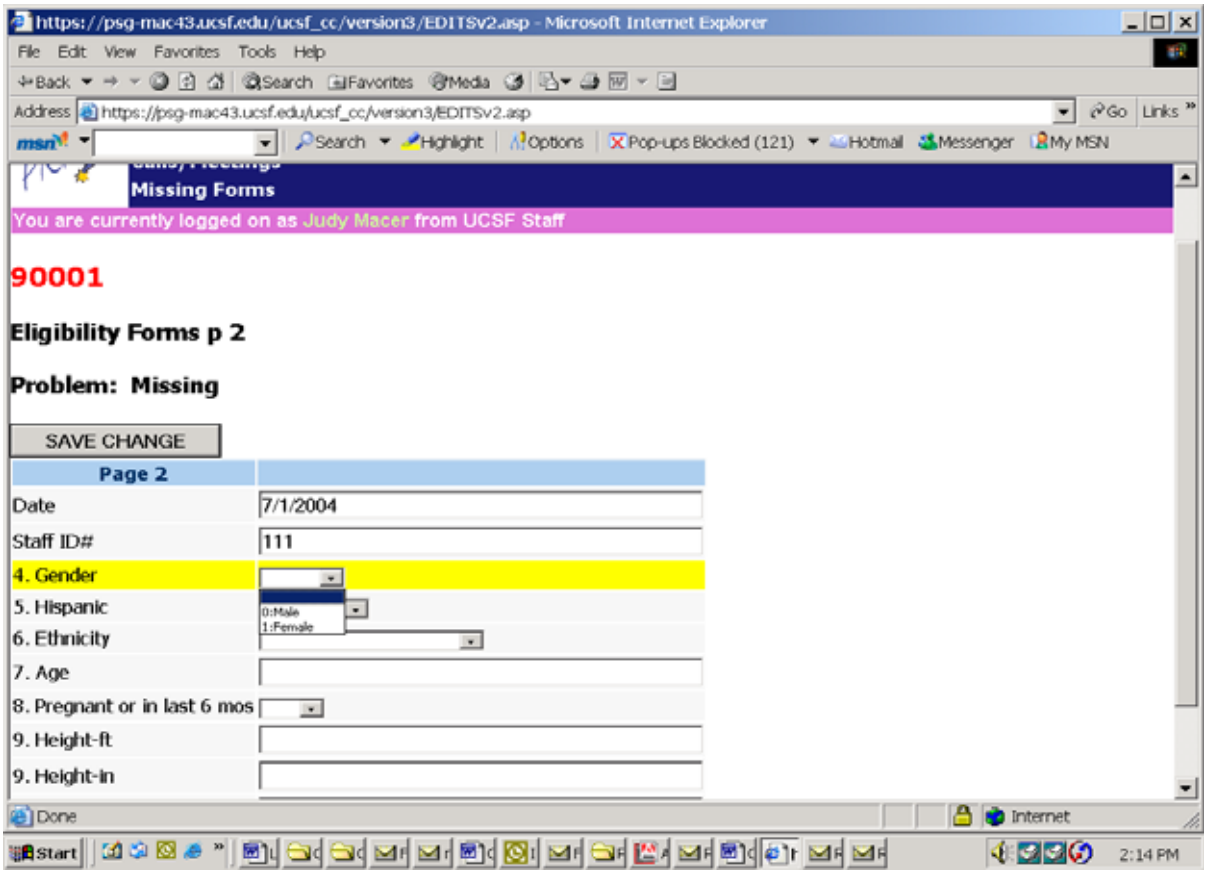
An overview of the process for resolving a query is outlined below:

1. Go to **Resolve Queries**

2. **Select query to be resolved** by clicking on red "go" button which will lead to the page containing the data that requires correction.

Make change. The question(s) that generated the query will be highlighted in yellow. However, any field on the screen can be changed. If there is a drop-

down list, please use it to select a response.



3. **Click on "SAVE CHANGE"** button. (This is a critical step!!!)

4. The database will be corrected and the query will disappear from this list the following day.

When resolving queries, please keep the following in mind:

- "Inconsistent" errors will be displayed with both of the inconsistent questions highlighted in yellow. The desired changes should be made and the "Save changes" button at the top of the page should be clicked. Note that the query listed in the **Resolve Queries** report disappears immediately upon saving the changes. However, the query program retests these data to ensure there are no further errors.

- No changes are saved until the "Save Changes" button at the top of the page is clicked. PRIDE fields use drop-down lists, allowing the user to choose

from a list of allowable answers, as well as fields that must be filled in directly. Thus it is possible to type in something that is inappropriate for a particular field (such as a number that is outside the allowable range). If an inappropriate entry is made it will not be saved to the database and a message will state that the change was not saved.

- Typically a highlighted field is the incorrect field and the data must be changed in that field. However, you may realize that an incorrect entry was made in another field on the same page (one that is not highlighted) and when that entry is corrected the highlighted field will be correct; therefore, any field on the screen can be changed.

18.8.3 Making "Comments"

Comments should be used only when a query cannot be addressed. They will cause the query to be removed from the edit report. There are four choices for the comment field:

Comment	**When to Use**
Not an error	"Not an error" is largely used to verify that "out of range" values have been checked and are indeed correct. Otherwise, "not an error" comment should rarely be used. **Note:** It is helpful to notify the Project Assistant at the Coordinating Center that the data queried was correct.
Irretrievable	If data is indeed missing, and there is no way to retrieve the information, "irretrievable" should be selected.
Participant ineligible	For "missing data" queries that reflect questions intentionally not answered because the participant became ineligibile, "participant ineligible" should be chosen.
Other	There may be occasions when the above three comments do not fit. Use "Other" for those situations.

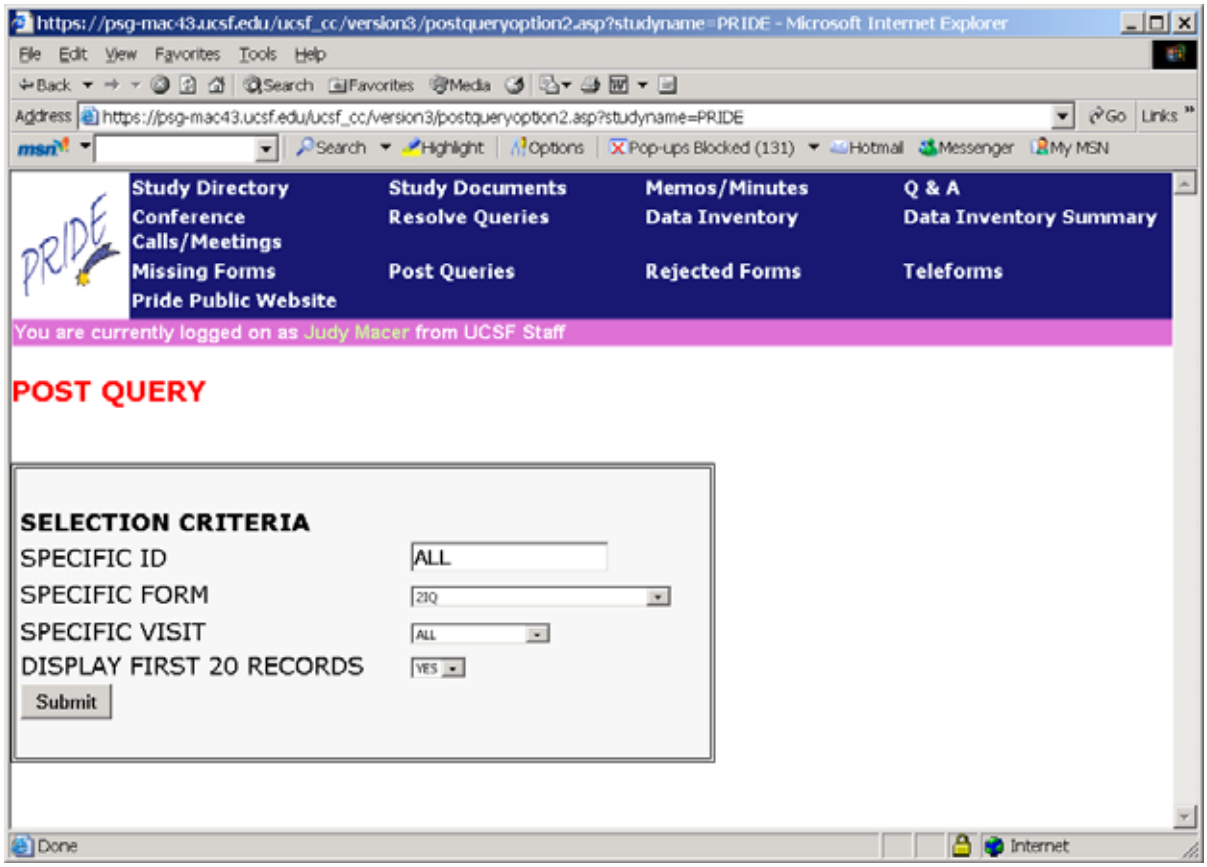
When the query-generator runs, it inspects the entire database. If a query has been addressed properly, it will not be re-generated by the program, (i.e., it will disappear from the edit report the next day. Therefore, a "comment" **should not** be

entered if a query can be "fixed".

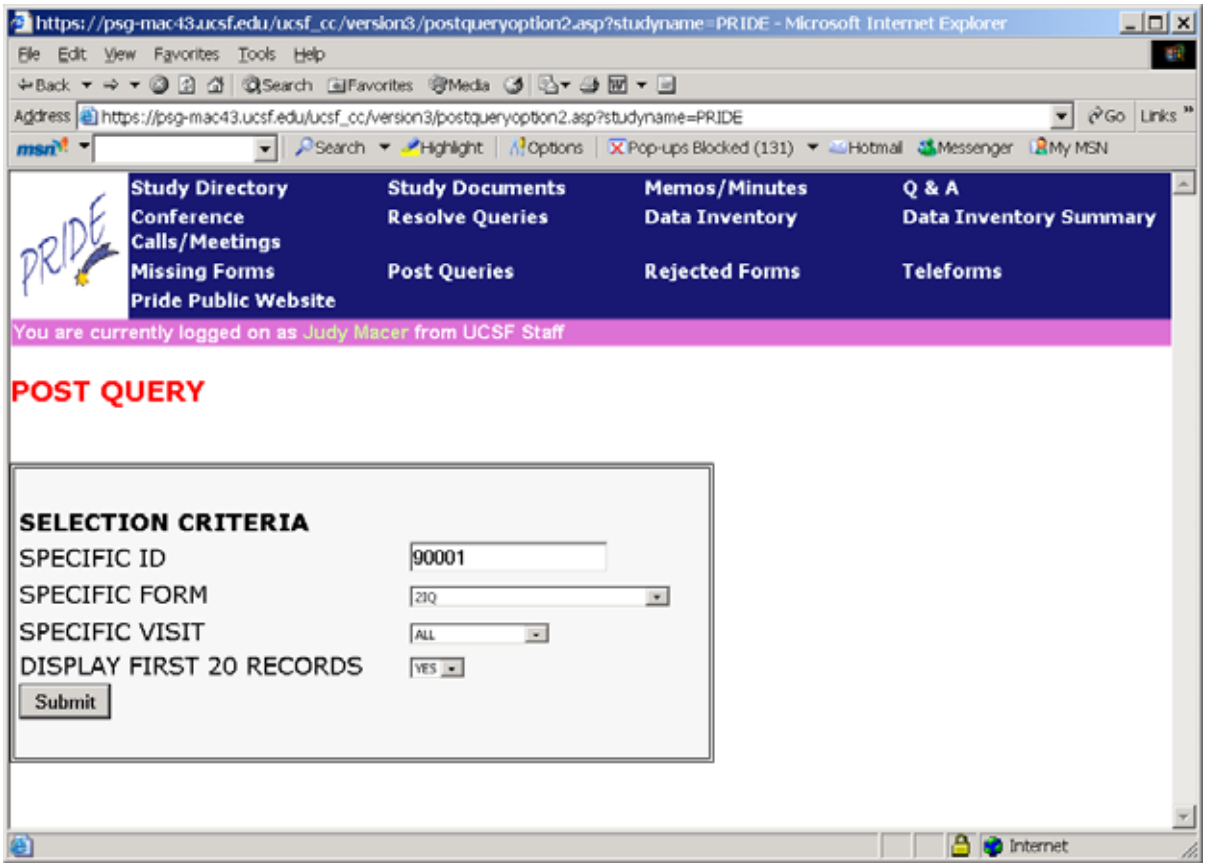
18.8.4 Posting a Query

The majority of queries will be generated by the DMG using the error checking programs. However, in some cases, site staff may want to change data that were entered on a form, faxed to the database and later discovered to be incorrect. To make the change to the database you must generate your own query, by using the **Post Query** option. The process of originating a query is as follows:

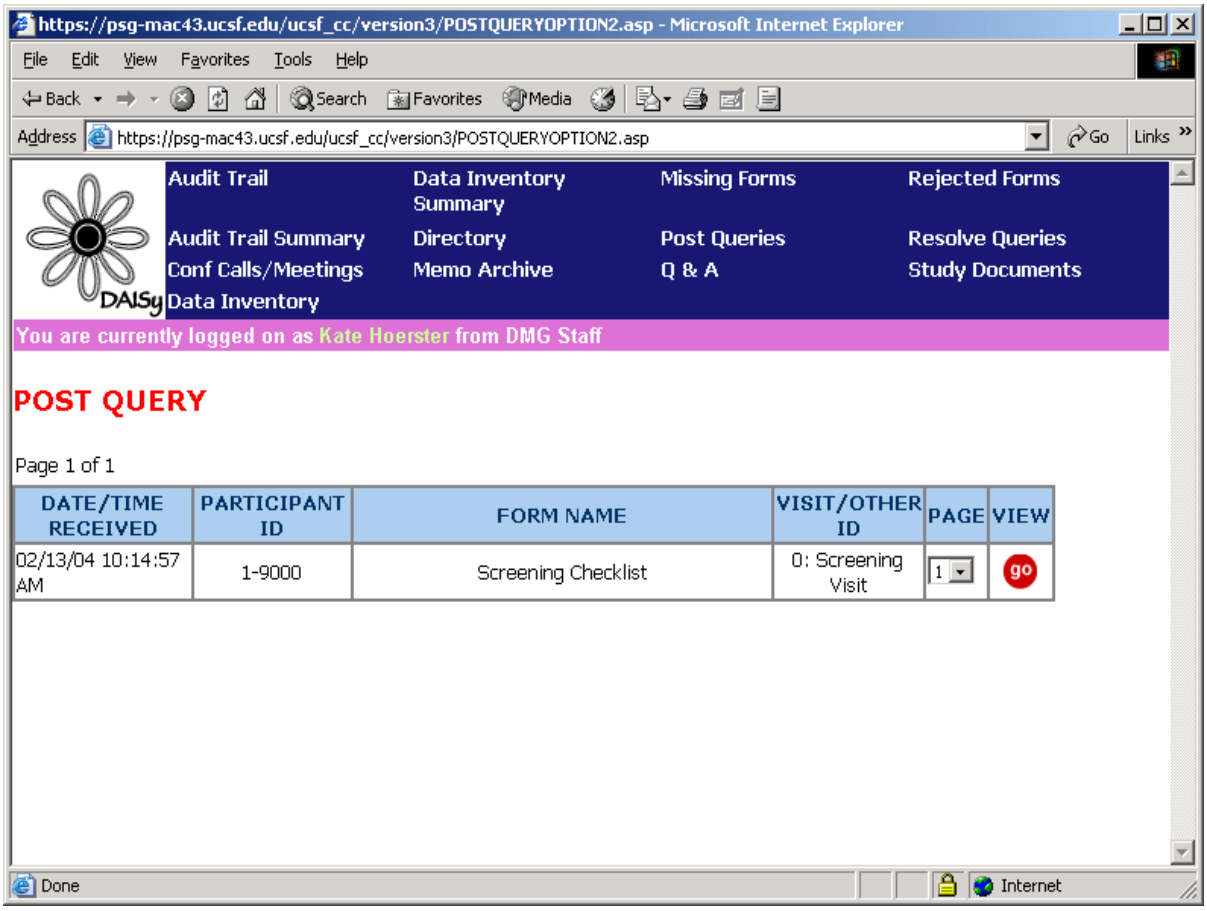
1) Click on the 'Post Query' link on the header bar



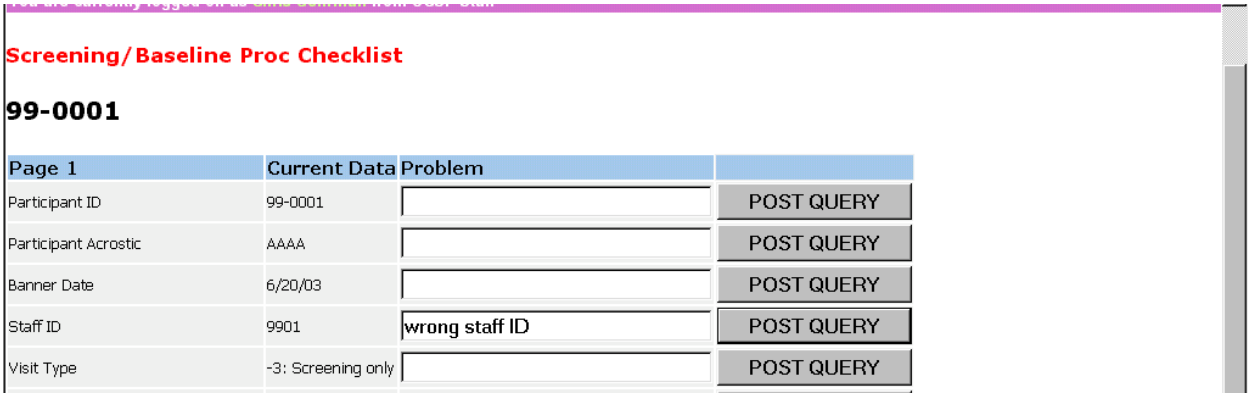
(2) Enter selection criteria for the participant and for which you want to address a query. In this case, you cannot select all; instead, a specific participant and form must be listed.



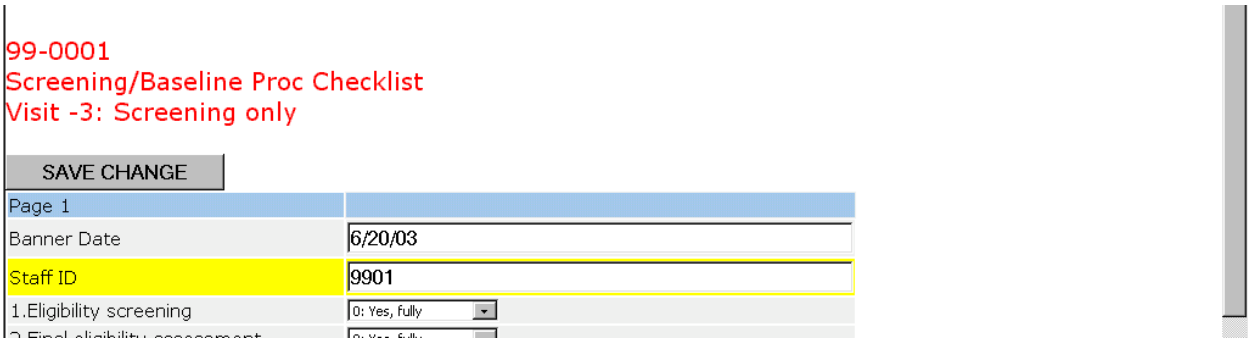
(3) Click on the red "go" bubble listed next to the form desired.



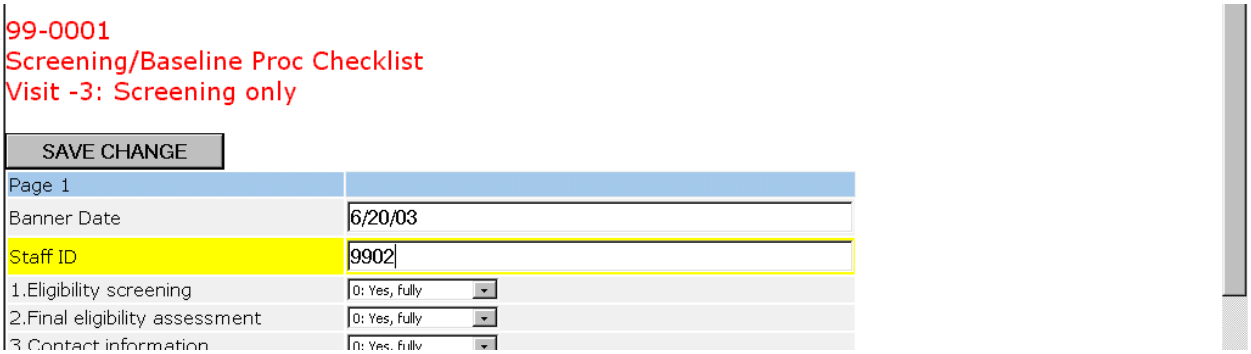
(4) Type in the problem or concern in the 'problem box.'



(5) Hit 'post query.'



(6) Make changes to data.



(7) Hit 'save change.'
(8) The change to the database has been saved.
NOTE: Always use a 4 digit year when changing dates.

18.8.5 Audit Trail

All changes made to the database are tracked and recorded in an "Audit Trail." The audit trail includes the User ID of the person making the change, the date and time, a description of the item changed, the old value, the new value, and the reason the change was made (name of the query). This report is primarily of interest for study auditors.

AUDIT TRAIL

Page 1 of 1

DATE	ID	FORM	VISIT	VARIABLE CHANGED	OPERATOR	OLD VALUE	NEW VALUE	REASON	COMMENT	ORIG
6/22/03 11:02:20 PM	99-0001	Screening/Baseline Proc Checklist	-3	Staff ID(SKSTFID)	dbo	9901	9902	wrong staff id (SKSTFID)		CC
6/22/03 10:46:29 PM	99-0001	Physical Exam	-3	1. EENT - abnormal specify(PEENTAB)	dbo	DIDN'T WANT TO DO IT	DIDNT WANT TO DO IT	Out of Range (PEDATE)		CC
6/22/03 10:46:29 PM	99-0001	Physical Exam	-3	Banner Date(PEDATE)	dbo	Jun 23 2003 12:00AM	Jun 20 2003 12:00AM	Out of Range (PEDATE)		CC
6/20/03 5:48:10 PM	99-0001	Vital Signs	-3	6. Weight(SVWEIGHT)	PSG\minotrain	181.5	131.5	nope, that was right (SVWEIGHT)		CC
6/20/03 5:46:57 PM	99-0001	Vital Signs	-3	6. Weight(SVWEIGHT)	PSG\minotrain	131.5	181.5	incorrect(SVWEIGHT)		CC

18.8.6 Audit Trail Summary

The audit trail summary lists the number of queries for each form in the database. It provides even more detail than the audit trail.

18.9 SECURITY PROCEDURES

Several levels of data security have been developed for the DMG Data System. Use of the PRIDE website is strictly limited to study staff. Each site will only have access to its own data. In addition, only limited staff from each site will be able to view data and address or generate queries.

Study staff members must not share their passwords with anyone else, including co-workers who may have trouble accessing the site or who have been locked out by repeated password errors. Such errors should be reported to the Coordinating Center Project Assistant, who will notify the DMG; they will respond as soon as possible and will attempt to fix the problem.

Any deviation from the security system requirements could compromise the system. **Do not share your password with anyone else.**

To ensure that the data are secure, the SQL server is backed-up nightly to digital linear tape and monthly copies are stored off-site. The server is physically housed in a limited access security room at UCSF.

18.9.1 Site Security Manager

Each site will have a security manager, usually the Study Coordinator. Any necessary changes to the secure data system (i.e., forgotten password,

removing web access, adding web access) must go through the site security manager. The security manager will request any changes for the site via email to the Project Assistant at the CC and should also send a duplicate request, which should be signed by security manager, by fax (415-353-9790). The DMG will track and verify changes to the security system.

In order to ensure the security of the study website, you must close Internet Explorer when you have finished using the PRIDE website. If you are going to use the Internet for other purposes, please close your browser and then re-open it.