URINARY INCONTINENCE TREATMENT NETWORK

BE-DRI

Behavior Enhances Drug Reduction of Incontinence

April 30, 2004

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A. STUDY AIMS

The primary aim of this study is to test if the addition of behavioral treatment to drug therapy for the treatment of urge incontinence will increase the number of patients who can discontinue drug therapy and sustain a significant reduction of incontinence (i.e., 70% fewer incontinence episodes compared to baseline).

Other study aims are to:

- test whether the effectiveness of drug therapy can be enhanced by combining it with components of behavioral intervention;
- determine the cost-effectiveness of combining behavioral and drug therapy in clinical practice; and
- examine the long-term durability of drug and behavioral treatments.

Bladder diaries completed by subjects before and after the treatment will be used to calculate reduction in the frequency of incontinent episodes. Secondary outcome measures will include frequency of daytime and nighttime micturition, urgency, patient satisfaction, quality of life, and costs.

B. BACKGROUND AND SIGNIFICANCE

B.1 Urge Urinary Incontinence: Prevalence and Impact

Of the estimated 16 million Americans who suffer from urinary incontinence (Fantl, Newman, Colling, & al, 1996), two-thirds are women. Individuals with incontinence suffer social isolation, sexual and relationship dysfunction, and depression (Hunskaar & Vinsnes, 1991). The monetary cost to society is over $26 billion annually; most of this money is spent on the consequences of incontinence, not on its treatment (Wagner & Hu, 1998). Urinary incontinence remains an under-reported and under-treated condition. Patients suffer in silence because they think incontinence is a normal part of aging, or they feel embarrassed to discuss the problem with their physician.

B.2 Treatment Options for Urge Incontinence

Among the interventions available for urge incontinence are drug therapies and behavioral treatments. Drug therapy is the most common approach, and anticholinergic drugs have been the most widely used medications for treatment of urge incontinence. Although drug therapies are known to be effective for reducing urge incontinence, many patients wish to discontinue use of these medications due to side effects, expense, and/or a simple desire not to be taking drugs.

Previous studies have shown that behavioral training is safe, effective, and yields high levels of patient satisfaction (Baigis-Smith et al, 1989; Burgio et al, 1985, 1998, 2002; Burton et al, 1988). In behavioral training, patients are taught to increase pelvic muscle strength and control and then to use voluntary pelvic floor muscle contractions to induce detrusor relaxation, increase bladder outlet resistance when they experience urgency, and prevent urge-related leakage.

B.3 Rationale for Combination Drug and Behavioral Therapy

A limitation of drug therapy is that few patients are actually cured. In a recent clinical trial, only 23% of patients were dry after treatment with individually titrated oxybutynin (Burgio

et al, 1998). Thus, there is a need for research to explore ways to enhance the effectiveness of drug therapies. One potential way to improve the efficacy of drug therapies for urge incontinence is to combine them with behavioral treatments. Because behavioral treatments are effective for reducing incontinence as stand alone therapies, it is likely that they would be effective for helping patients withdraw from drug therapy. Some clinicians combine these treatments with the idea that relaxing the bladder with a pharmacologic agent provides a measure of control that will allow the patient to be able to better learn volitional control of detrusor contraction. Some clinicians point to the hypothesis that drugs help to inhibit detrusor contraction, but that patients will not become dry without their own efforts exercised to suppress the bladder and reach the toilet in time to void. Having learned better control of the pelvic floor muscles, it is thought that patients who receive behavioral intervention could be more successful in withdrawing from drug therapy, because they will have new skills to help them avoid accidents when they are no longer taking their medication. On the other hand, patients who have not learned pelvic floor muscle control may be more likely to regress when drug therapy is withdrawn.

There are two reasons to believe that combining drug and behavioral treatment might enhance patient outcomes. First, although the mechanisms by which these respective therapies work have not been established completely, there is evidence that they operate by different means, suggesting that they may have additive effects (Goode et al, 2002). Previous research has shown that change on urodynamic parameters, such as bladder capacity or detrusor instability, may be mediators of change with drug therapy (Goode et al, 2002) but is clearly not necessary for improvement of incontinence with behavioral intervention. Second, there is some evidence of significant added benefit of combination therapy. In one study (Burgio et al, 2000), patients who were not dry or completely satisfied after behavioral or drug treatment were offered crossover into combined therapy. The data suggested an added benefit of combination therapy in these patients. The results were encouraging but are not considered definitive due to the small sample size and issues with selection bias. A recently reported trial by Mattiason et al, (2003) found that a simple bladder training program provided a modest increase in the effectiveness of tolterodine in patients with an overactive bladder. However, patients in that trial were not necessarily incontinent and received the behavioral treatment in written format only. Therefore, while supportive of a combined therapy approach, the findings provide a conservative estimate of the potential effect of combined therapy versus drug alone in an incontinent population.

Little is known of the effectiveness, the potential, or the acceptability of combining therapies for incontinence, and this study will address this gap in knowledge.

B.4 Cost-effectiveness of a Combination Therapy Approach

Urinary incontinence is a common, debilitating, and costly problem in women. The most recent estimate of the annual direct costs of incontinence in all ages is $16 billion (1994 dollars) (Fantl et al ,1996;Wilson et al, 2001) with the largest cost category being routine care (pads, protection, laundry; 70% of costs for women), followed by nursing home admissions (14%), treatment (9%), complications (6%) and diagnosis and evaluations (1%).

A majority (50-75%) of the cost of incontinence is attributed to routine care (Wilson et al, 2001), which varies widely between studies and is reported as $2 to $21 per week (Ouslander and Kane, 1983; Sowell et al, 1987; Wyman, 1997; Dowell et al, 1999; Wagner and Hu, 1998; McClish et al, 1999). However, there are minimal primary data quantifying these costs or the effect of incontinence severity on costs and there are no data on the change in routine care costs following treatment for incontinence.

There is a small but growing body of literature on patient preferences (called utilities) and willingness to pay (hereafter called "preferences") for improved health. To date, there are minimal data on preferences in incontinence and no data on the effect of treatment or change in incontinence severity on preferences. However, incontinence is one of the three chronic health conditions that most adversely affects utility scores (Alzheimer's disease [0.58], stroke [0.68], urinary incontinence [0.70]) (Mittman et al, 1999). The proposed study would be the first detailed analysis with data before and after treatment of utilities and willingness to pay for women with urge incontinence.

Increasing costs of medical care have led health care decision makers to evaluate new tests and therapies to compare value for the cost (Gold, 1996). The most common measure is the cost-effectiveness ratio that incorporates data on both health outcomes and costs to comprehensively describe the relative value of alternative interventions. Cost-effectiveness analyses (CEA) in urinary incontinence have focused on strategies for nursing home management and comparison of surgical techniques for stress incontinence (Ramsey et al, 1996). The only CEA on urge incontinence is a Canadian study examining the cost-effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin (O'Brien et al, 2001). The investigators estimated that the incremental cost per quality adjusted life year (QALY) was Can $9,982, well within currently accepted benchmarks for cost-effectiveness. Prior studies are limited by lack of primary data on costs, probabilities and utilities, which this proposed study will provide.

B.5 Durability of Drug and Behavioral Treatments

Although behavioral treatment and drug therapy have each been shown to be effective in the short term, it is not known if drug therapy maintains a consistent effect over time. It is also not known if patients continue to take their medication, perform pelvic floor muscle exercises, or employ behavioral strategies to manage urgency over the long term. Further, it is not known if bladder control problems return, or if subjects eventually seek other types of continence treatments. Therefore, this study proposes to collect follow-up data for at least 6 months after treatment and potentially every 6 months for the duration of the UITN.

C. METHODS

C.1 Study Design

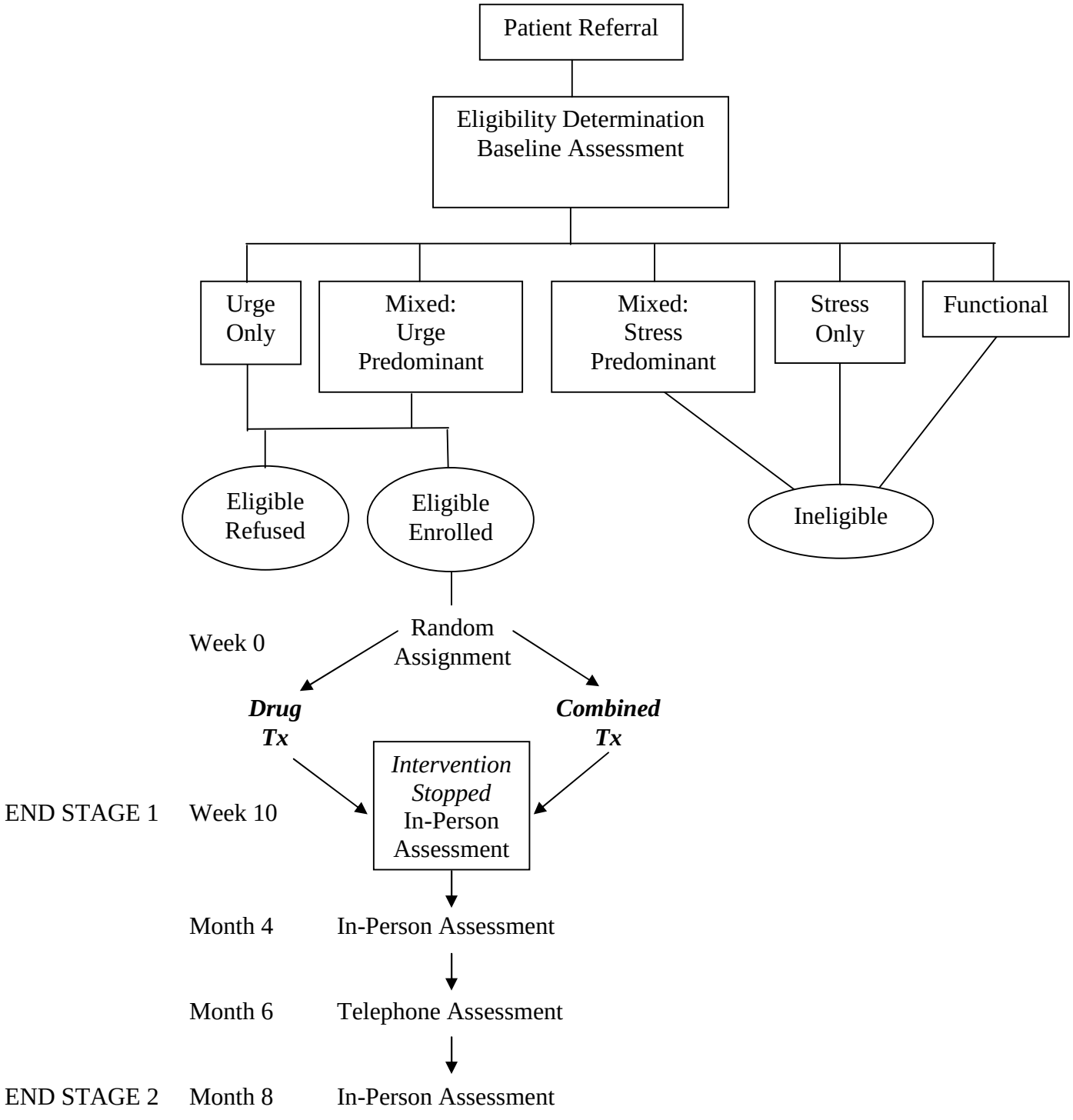
C.1.1 Design and Study Schema

As depicted in Figure 1, the design of the study is a two-stage randomized clinical trial to compare the effects of two interventions, drug therapy alone and combination drug therapy and behavioral treatment, on the frequency of urinary incontinence and success in withdrawing patients from drug therapy. Using stratified and blocked randomization procedures, subjects will be assigned to 10 weeks of drug or 10 weeks of drug combined with behavioral treatment. In order to assure between-group comparability on pre-treatment type and severity of incontinence, subjects will be stratified on two factors: type of incontinence and severity of incontinence. Baseline bladder diaries and patient history will be used to classify incontinence as urge only or mixed urge and stress incontinence. Mixed urge and stress incontinence will be diagnosed when subjects report episodes of both urge and stress incontinence on the MESA questionnaire and/or document both in the bladder diary. Baseline bladder diaries documenting the frequency of incontinence will be used to assign subjects to one of two frequency groups: lower incontinence frequency (<14 episodes of urinary incontinence per week) or higher incontinence frequency ($\geq$

14 accidents per week). Within each of the four strata formed by these two characteristics of incontinence, blocked randomization will be performed to avoid inequity in the total number of subjects assigned to each random size group.

In Stage 2, after 10 weeks of primary treatment, drug therapy will be withdrawn in both groups and behavioral treatment sessions stopped in the combination arm. The effects of drug withdrawal on continence status will be measured at study month 8 (i.e., 5.5 months after cessation of primary treatment).

Figure 1. Trial Design



C.2 Definition of Treatment Success

The primary outcome measure will be a composite endpoint that will assess "successful drug withdrawal" defined as:

1. not taking drug or receiving other urge UI therapy (i.e., neuromodulation, botox injections, myomectomy, electrical stimulation, or any intravesical therapy) and not taking a tricyclic antidepressant or duloxetine at 8 months; and
2. a ≥70% reduction in number of incontinent episodes as compared to baseline.

Although treatment success will be evaluated at several time points, the a priori primary endpoint for evaluating success is at 8 months.

C.3 Study Population

C.3.1 Eligibility Criteria

Subjects for this study will be community-dwelling women with pure or predominant urge incontinence.

a. Inclusion Criteria

1. Female
2. Pure or predominant urge incontinence as evidenced by MESA urge symptom score (percent of total possible urge score) greater than MESA stress score (percent of total possible stress score)
3. Incontinence frequency of at least 7 times per week, per 7-day bladder diary
4. Persistent incontinence for at least the three previous months*
5. Available for 8 months of follow-up and able to complete study assessments, per clinician judgment
6. Signed informed consent form

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

b. Exclusion Criteria

1. Age <21 years
2. Pregnancy by self-report or positive pregnancy test, or self-reported intention to become pregnant in the next 8 months
3. For women of child-bearing age or ability, refusal to use medically acceptable means of birth control for duration of the study
4. <6 months post-partum*†
5. Inability to contract pelvic floor muscles during evaluation
6. Previous extensive behavioral/biofeedback treatment within the past 2 years (i.e., participation in a formal program of behavioral therapy of at least 2 months duration)
7. Reported continual leakage or always being damp
8. Hypersensitivity to study drug (Detrol LA)
9. Systemic disease known to affect bladder function (e.g. Parkinson's disease, multiple sclerosis, spina bifida, spinal cord injury or trauma)
10. Fecal impaction (on rectal examination); may be enrolled if urinary incontinence persists after the bowel problem is managed
11. Urinary tract infection (defined as ongoing treatment for UTI); patients with UTIs cannot be screened for BE-DRI until they are 7-days post treatment and have no persisting symptoms/Investigator thinks the UTI is resolved

12. Current catheter use to empty bladder
13. Post-void residual volume greater than 150 ml
14. Urethral diverticulum, current or previous (i.e. repaired)
15. Prior augmentation cystoplasty or artificial sphincter
16. Neuromodulation for pelvic indications
17. Current use of anticholinergic agents; must have been off such drugs for at least 4 weeks
18. Current use of tricyclic antidepressants; must have been off such drugs for at least 4 weeks
19. Current use of duloxetine; must have been off this medication for at least 4 weeks
20. Current use of cholinergic agonists
21. Current diuretic use with dosage change within last three months
22. Uncontrolled medical problem (e.g. poorly controlled diabetes, decompensated congestive heart failure); may be enrolled if and when the condition is stabilized appropriately
23. History of bladder or pelvic CA or pelvic radiation therapy
24. Glaucoma without ophthalmologist clearance
25. Patients with hematuria, defined as a positive dipstick and >5 RBC/high power field OR a micro result of >5 RBC/high power field, who have not had an AUA workup within 5 years
26. Gastric retention (by medical history)
27. Treatment of vaginal prolapse with a pessary or incontinence dish that has not been stable for the past 3 months
28. Incontinence, vaginal, bladder, and/or prolapse surgery within the past 6 months
29. Non-ambulatory (ambulatory with assistive devices does not exclude the patient)
30. Participation in another treatment intervention trial that might influence the results of this trial.

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

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

C.4 Randomization

Eligible patients will be randomized at Visit 1 (i.e. the visit during which treatment is initiated) using a web-based randomization system at the Biostatistical Coordinating Center. In the event of technical problems, a back-up randomization envelope system will be utilized.

As described in C.1, patients will be stratified on two factors: type of incontinence and severity of incontinence. Within each stratum, blocked randomization will be performed to avoid inequity in the total number of subjects assigned to each group.

C.5 Treatments

C.5.1 Drug Therapy

The drug therapy selected for use in the BE-DRI trial is a 4mg daily dose of tolterodine tartrate extended release capsules, trade name Detrol LA. Drug therapy will be considered complete if a patient remains on drug for a minimum of 9 weeks.

It is possible that a patient will not be able to tolerate the study drug at the 4mg dose.

Uniform interventions have been developed for the common side effects of dry mouth and constipation for use study-wide. All other bothersome side effects will be treated at the discretion of the study physician or interventionist. The daily dose of Detrol LA 4mg may be decreased to 2 mg if all other palliative interventions fail to reduce side effects to a tolerable level. Detrol LA may be discontinued at the discretion of the study physician and interventionist if the patient continues to suffer from intolerable side effects.

Drug therapy will be conducted in 4 visits across 10 weeks. During this 10-week period, one break from drug treatment of ≤7 days is allowable, recognizing that such a break might be clinically indicated; e.g. during treatment of another illness.

Visit #1: A baseline symptom checklist will be completed and patients will be given a 30-day supply of study drug**.** A Detrol LA Information Handout developed specifically for this trial will also be provided along with standardized instructions on fluid management.

Visits #2, #3, #4 (at 2-3 week intervals): The patient will return to clinic for an assessment by a health care professional including administration of a symptom checklist. Minor side-effects will be treated symptomatically. Pill counts will be performed at each treatment visit to check for drug adherence. At the point at which the drug supply is inadequate to cover the days until the next visit, patients will be provided with another 30-day supply of study drug.

At the end of 10 weeks, drug therapy will stop.

For the details of the drug-only intervention protocol, refer to Appendix C.

C.5.2 Combination Therapy (Drug and Behavioral Treatment)

Combined behavioral and drug treatment will also be conducted in 4 visits across 10 weeks. Patients will receive both behavioral treatment and drug therapy (as described above). The behavioral treatment will include teaching pelvic floor muscle control and exercise; adaptive responses to the sensation of urgency and techniques to avoid urine loss and manage urgency; and bladder training to increase voiding intervals for those who void >8 times/day. Later visits will be used to individualize and reinforce patient's effort. Training will be supplemented with verbal and written instructions for home practice to be conducted daily between clinic visits.

At the end of 10 weeks, both drug therapy and behavioral treatment sessions will be stopped. Patients will be instructed to continue pelvic floor muscle exercises and behavioral strategies independently in order to maintain treatment effect.

For details of the combined drug and behavioral treatment protocol, refer to Appendix B.

C.5.3 Standardization of Treatments

To ensure standardized administration of both drug treatment and drug combined with behavioral treatment across clinicians and across clinical sites, interventionists will be trained and certified centrally. Subsequent training meetings will be organized as necessary to ensure that skills are maintained.

C.6 Measures

C.6.1 Primary Outcome Measures

a. Drug Withdrawal

Successful withdrawal from drug will be determined from medical records and/or patient report and will be defined as cessation of drug at 10 weeks (i.e., at the end of Stage 1) and no request for this or any other drug or other therapy (i.e., behavioral, neuromodulation, botox injections, myomectomy, electrical stimulation or any intravesical therapy) to treat urge

incontinence after 10 weeks (i.e., after the end of Stage 1). NOTE: As tricyclic antidepressants have significant anti-cholinergic effects and therefore could influence bladder function, a patient who begins taking such a medication while in this study, regardless of the indication, will be considered a treatment failure. Similarly, as duloxetine is indicated for treatment of stress urinary incontinence, a patient who begins taking this medication while in this study will be considered a treatment failure.

b. Bladder Diary

Successful percent reduction in number of incontinent episodes is defined as $\geq$ 70% and will be calculated as the change in the number of incontinent episodes per week at follow-up as a percentage of the baseline rate. Number of incontinent episodes will be collected using a bladder diary. Self-monitoring of voiding behavior and frequency using a daily dairy is a practical and reliable method for assessing the frequency of voluntary micturitions and involuntary episodes of urine loss (Locher, Goode, Roth, Worrell, & Burgio, 2001; Nygaard & Holcomb, 2000; Wyman, Choi, Harkins, Wilson, & Fantl, 1988). For purposes of this trial, a 7-day bladder diary will be used. The diary will be used to record the following:

- time of every void;
- time of every episode of urine loss;
- bed times and awake times;
- volume of all fluid intake and each void for 2 days (intake and output);
- size of the urinary accident (defined as small [damp pad or few drops], medium [wet pad or underwear] or large [soaked pad or outer clothing]);
- reason for the urine loss or circumstances of the accident (with emphasis on discriminating urge accidents from stress or other accidents); and
- sense of urgency experienced with each void or episode of urine loss on Days 1 and 7.

A minimum of 5 days of complete data is required for a bladder diary to be considered valid. If not valid, the diary must be repeated.

C.6.2 Secondary Outcome Measures

a. Urinary Symptoms

Three symptoms are of interest: frequency of urination and nocturia (as measured by the bladder diary) and urgency (as measured by the International Urgency Severity Scale: Bowden et al, 2003).

b. Quality of Life

Because no direct relationship has been reported between a patient's level of distress and a patient's level of satisfaction with treatment, it will be important to measure the impact of treatment outcome on the patient's quality of life (QOL). Health-related QOL is a multidimensional concept that encompasses well-being that is related to health and is distinguished from measures of health and functional status. A condition-specific measure will be used in this trial so as to be sensitive enough to detect change, i.e. the *Incontinence Impact Questionnaire* (IIQ) and the *Urogenital Distress Inventory* (UDI) developed by Shumaker et al (1994). The former measure assesses the impact of UI on various activities, roles, and emotional states, whereas the latter measure assesses the degree to which UI symptoms are troubling to women. Adequate validity, reliability and sensitivity to change have been reported by the authors. In addition, the Overactive Bladder Questionnaire (OAB-q) will be included as a disease specific measure of health related QOL and bother, developed specifically for continent and incontinent patients with overactive bladder (Coyne, 2002). Finally, the *SF-12* will be included

as a general measure of health-related QOL (Ware et al, 1996). This shortened version of the Short Form Health Survey (SF-36) has demonstrated validity and reliability and provides two subscale scores (mental health and physical health).

c. Satisfaction with Treatment

Due to the increasing concern regarding patient satisfaction with medical care and the documented association between satisfaction and treatment adherence (Lochman, 1983), patient satisfaction has been included as a secondary outcome. Data collected in a study of behavioral treatment by Burgio et al (2002) indicate that patients are satisfied with treatment outcomes if there is an approximate 70% reduction in incontinence episodes. The questions used in that study will be used in this trial; for example, "How satisfied are you with your progress?" and "Overall, do you feel that you are much better, better, about the same, worse, or much worse?"

d. Pelvic Floor Assessment

Pelvic muscle strength will be assessed at baseline, 10 weeks, and 8 months, using the digital test of Brink et al (1994). This test produces a 9-point scale based on strength, duration and movement observed with muscle contraction.

e. Return to Drug or Other Urge UI Treatment

It is possible that patients who are off drug at 10 weeks will subsequently return to drug use (including drugs other than Detrol LA) or request and receive other therapies (i.e., behavioral, neuromodulation, botox injections, myomectomy, electrical stimulation or other intravesical therapy) for urge incontinence during the long-term follow-up period. Therefore, this will be monitored at each visit. In addition to tracking incidence of return to drug or receipt of other therapies, patients also will be asked the reason for resuming drug or receiving other urge UI treatment.

f. Costs

1) **Incontinence Expenses** Participants will record numbers of pads, protection, laundry, dry cleaning, personal hygiene products, household protection, and household cleaning products consumed specifically for their incontinence. They will also record indirect resources related to incontinence (time spent on incontinence-related healthcare, limits on employment or volunteer work due to incontinence). The Incontinence Expense questionnaire was derived from other published expense surveys and has been validated in a study of over 300 women with incontinence (analyses in progress) (Fantl et al, 1996;Dowell et al, 1999). The average national cost of each product will be determined by a survey of several retail and wholesale stores.
2) **Medical Care Utilization** Medication use will be determined from the trial and cost will be estimated using the minimum average wholesale price of commonly prescribed medications (Cardinale, 1997). Marginal use of resources (provider visits) will be estimated for the drug therapy alone vs. drug therapy combined with behavioral treatment groups. Direct costs will be calculated using a proxy for societal cost, Medicare resource-based relative value scale charges for physician services (Health Care Consultants of America, 2000).
3) **Utilities** Patient preferences (also called utilities for states of health) associated with urge incontinence will be measured with the Health Utilities Index Mark 3 (HUI3). This measure provides a rapid and reproducible quantification of utilities for health states (Feeny et al, 1995; Furlong et al, 1998). The HUI3 is a generic health status and health-related quality of life (HRQL) measure based on standard gamble theory that is well tested both in clinical and population health studies. The HUI3 has fifteen multiple

choice questions or attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) with five to six severity levels per attribute, ranging from highly impaired to normal. These categorical data on health status can be translated into a utility score that reflects global HRQL (Furlong et al, 1998).

4) **Willingness to pay for Incontinence Improvement** Willingness to pay for improvement in incontinence severity reflects the value an individual places on a specific health state by estimating the maximum dollar amount she would pay for health-improving interventions. We will ask women to place a monetary value on both improvement of $\geq$ 70% and cure of incontinence. We will also quantify willingness to pay as a proportion of yearly income. This instrument was designed for the ongoing UITN Protocol #1 and is based on previous work in urinary incontinence (Kobelt, 1997).

C.6.3 Independent Variables

There are five groups of independent variables to be collected at baseline:

a. Sociodemographic characteristics: age; race; marital status; education; occupation; annual income; insurance status

b. Risk factors for UI: age (Milsom et al, 1993; Yarnell et al, 1981, 1982); parity (Burgio et al, 1996; Foldspang et al, 1992; Jolleys, 1988; Sommer et al., 1990; Thomas et al, 1980); weight of largest baby; use of HRT (Burgio et al., 1991; Jolleys, 1988); BMI (Brown et al., 1996; Burgio et al., 1991; Mommsen & Foldspang, 1994; Yarnell et al., 1982); previous anti-incontinence surgery and gynecologic surgery (Jolleys, 1988; Milsom et al., 1993); current medications (Montella & Wordell, 1996); and childhood or family history of enuresis (Jarvellin et al, 1988; Steinhausen and Gobel, 1989; Rittig, 1995).

c. Type and severity of UI measured by the following: MESA questionnaire (Herzog et al., 1990); 7-day bladder diary

d. Pelvic floor muscle strength measured at baseline, 10 weeks and 8 months by the digital test of Brink et al (1994)

e. History of previous treatment for incontinence

C.6.4 Intervening Variables

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

a. Pelvic comorbidity: pelvic organ prolapse (POP-Q quantification; Bump et al, 1996)

b. Side effects of drug: self-reported symptoms at each visit.

c. Adherence to behavioral treatment: As described in section C.4.2, during the 10-week treatment period, patients will be asked to report the weekly frequency of exercise sessions and the number of sphincter exercises practiced in each session. In Stage 2, at each visit, patients will be asked how often each week they do pelvic floor muscle exercises and on average how many exercises they do each time.

d. Adherence to drug therapy: At each of the 4 intervention visits, a pill count will be done to determine the number of pills taken between visits.

C.7 Assessment Procedures

A schedule of measurements is included in Appendix A. All patients, including patients defined as treatment failures, will be asked to complete all study visits.

C.7.1 Baseline Assessment

The first study visit will include several measures to determine eligibility and to collect baseline data. A history and physical examination will be completed. The history will query

medication use and medical conditions (e.g. glaucoma, gastric retention) and events that may have implications for intervention. The physical examination will include measurement of height and weight; pelvic and rectal examination; targeted neurological examination (deep tendon reflex, perineal sensation, and anal sphincter voluntary contractions); and urinalysis. Pelvic examination will include prolapse assessment (POP-Q) performed according to the guidelines established by the International Continence Society (Bump et al., 1996), and pubococcygeus muscle strength assessment (Brinks). Self-administered measures include the MESA (Herzog et al, 1990) and UCSF questions about incontinence symptoms, the quality of life measures (the Incontinence Impact Questionnaire [IIQ], Urogenital Distress Inventory [UDI], Overactive Bladder Questionnaire [OAB-q], and SF-12 Health Survey), and Incontinence Expenses the Health Utilities Index and Willingness to Pay Instruments. The 7-Day self-administered baseline bladder diary has four purposes:

1) to document whether the subject is eligible for treatment on the basis of having had at least 7 accidents per week and able to complete valid 7-Day bladder diaries;
2) to assist in discriminating urge incontinence from stress and other incontinence;
3) to determine the pre-treatment frequency of incontinent episodes, providing a basis for calculating treatment outcome; and
4) to determine pre-treatment micturition frequency.

NOTE: All baseline measures must be repeated if a patient is not randomized within 3 months of completing these measures.

C.7.2 End of Stage 1 Visit (10 weeks)

An end-of-treatment bladder diary will be collected at the 10-week visit. The Patient Satisfaction Questionnaire, the Incontinence Impact Questionnaire (IIQ), the Urogenital Distress Inventory (UDI), the Overactive Bladder Questionnaire (OAB-q), and the SF-12 Health Survey either will be completed by patients prior to the visit and returned at the visit or completed during the visit. A symptoms checklist and medication audit will be completed.

After this 10-week visit, drug therapy will be withdrawn in both groups. Subjects receiving behavioral treatment will be instructed to continue voluntary pelvic floor muscle exercise and strategies in order to maintain treatment effects. No further intervention visits for the behavioral treatment will occur.

C.7.3 Stage 2 Assessments

Patients will return to clinic for reevaluation of their continence status, satisfaction, and quality of life at 4 months and at 8 months post-randomization. If the patient prefers to conduct her 4 month visit by phone, that will be allowed. An intervening telephone contact will be made at 6 months post-randomization. At these visits, their drug status (on/off) and/or use of any other urge UI therapies will be determined. Prior to each contact, they will be mailed a set of questionnaires for completion, including the 7-day bladder diary, the Symptoms Checklist, the patient satisfaction questionnaire, IIQ, UDI, OAB-q, SF-12, HUI3, and the incontinence expenses and willingness to pay questionnaire. Patients in the combined group will also be asked to complete the exercise adherence questionnaire. Patients will be asked to return the completed questionnaires in-person if a visit is scheduled or by mail in a stamped return envelope. The questionnaires (except the bladder dairy) can also be completed during the study visit.

Patients who would "fail" because of a request to go back on drug must first be evaluated by a study physician to rule out the presence of a urinary tract infection (UTI) that could be causing UI symptoms. If a UTI is suspected, it should be treated and the respective follow-up

visit measures repeated once the infection is resolved. If after appropriate evaluation and/or treatment of a suspected UTI a patient still requests to go back on drug, she will be provided 2 months of drug at no cost. This option will be presented to patients after the decision to resume drug therapy in order to avoid potential bias introduced by the "benefit" of free therapy. If Detrol LA is contraindicated, an alternative anticholinergic drug will be provided.

C.7.4 Long-Term Follow-Up

Contingent on available funds, after Stage 2 ends, patients will be followed every 6 months for a total follow-up period of 26 months post-randomization. The measures for these three additional visits will be the same as for the 8-month visit, excluding the POP-Q and the pelvic floor muscle assessment, and can be administered by mail and/or telephone.

C.8 Statistical Considerations

C.8.1 Definition and Justification of Primary Endpoint

The primary endpoint for this study will be successful discontinuation of drug therapy and remaining continuously off anti-incontinence medications from Week 10 to the Month 8 visit (and not requesting a prescription for drug during this time or requesting any other kind of therapy to treat urge incontinence [i.e., behavioral, neuromodulation, botox injections, myomectomy, electrical stimulation or any intravesical therapy] or starting a tricyclic antidepressant or starting on duloxetine), and a 70% or greater reduction from baseline in incontinence episodes at Month 8. Thus, a successful outcome is a composite of two measures: drug discontinuation and efficacy. A patient who stays off drug and any other treatment for urge UI (including protocol prohibited medications with anticholinergic properties) but does not achieve a ≥70% reduction in incontinent episodes, or who does achieve a ≥70% reduction in incontinent episodes but does not stay off of drug and/or other treatments for urge UI, will not be considered a success for the primary endpoint. For purposes of assessing the primary endpoint, the writing of a prescription for an anti-incontinence medication at or after the Week 10 visit will be considered the same as resuming drug therapy, even if the prescription is not filled, or is filled but the drug not taken. Also, regardless of indication, any patient that begins use of a tricyclic antidepressant or duloxetine during this study will be considered a treatment failure.

The use of a ≥70% reduction in incontinence episodes as a criterion for efficacy is based on an observed association between this level of efficacy and satisfaction with treatment in data from a prior clinical trial for urge incontinence (Burgio et al, 2002). (The analyses of data from this trial that appear below were performed from original trial data and do not appear in the published trial report.) Women in the trial were asked how satisfied they were with their progress and how much better they felt compared with prior to treatment. Table 1 shows the percentages of women who were "completely satisfied" and who felt "much better," as a function of the level of reduction in incontinent episodes. In order to maximize the applicability of results to women in the current trial, the analyses are restricted to women with >7 incontinent episodes per week at baseline.

The table demonstrates that a 70% or greater reduction in incontinent episodes is associated with a high level of satisfaction. There is a suggestion of a "plateau" in satisfaction once efficacy reaches a 70% level, i.e., higher levels of efficacy do not seem to translate into higher levels of satisfaction.

Table 1. Satisfaction as a function of the level of efficacy achieved. Satisfaction is measured by whether the patient reports being "completely satisfied" and "feeling much better." Efficacy is measured by the percentage reduction in incontinence episodes from baseline to the end of an 8-week treatment period, based on bladder diaries.

percent reduction[a]	N[b]	percent "completely satisfied"	percent "feeling much better"
≤50%	23	41%	13%
50-60%	9	67%	11%
60-70%	15	53%	33%
70-80%	14	86%	79%
80-90%	16	80%	56%
90-100%	40	89%	80%

[a]Percentage reduction in incontinent episodes compared with baseline
[b]Because not all women answered both questions, a few of the sample sizes are 1 or 2 smaller

C.8.2 Sample Size

It is felt that in order to make up for the extra time, cost, and other demands on the patient and physician that behavioral therapy would introduce, the probability of achieving a primary endpoint "success" should be at least 20 percentage points higher with combined (drug combined with behavioral therapy) therapy compared with control (drug only) therapy. Expressed another way, if 100 women were all treated with either combined therapy or drug alone, we would want an extra 20 successes with the combined therapy approach in order to make it worthwhile. Therefore, the trial will be designed to have high statistical power for detecting a 20 percentage point treatment difference.

It is projected that the probability of a primary endpoint success with control therapy will be at least 10% due to increased fluid management and an awareness of voiding brought on by participating in the clinical trial. However, there is considerable uncertainty in this projection and the percentage could be much higher. To be conservative for purposes of clinical trial design, a variety of control rates were considered and the one leading to the largest required sample size will be assumed. This occurs when the success rates in the two treatment groups are symmetric around 50%, namely 40% and 60%. Assuming a two-sided α=.05 Fishers' exact test and no missing data, 242 patients (121 per group) are required to achieve 85% power for this treatment difference. Inflating this sample size for missing data, early treatment failures due to an inability to tolerate the drug, and for the slight loss in power from applying an early stopping rule (described below), a total sample size of 300 is projected.

Another important endpoint is a measure of short-term efficacy, the percentage reduction in incontinent episodes from baseline to the end of Stage 1 (Week 10). Data from a prior clinical trial of behavioral therapy (Burgio et al, 2002) provide estimates on which to base sample size calculations. Women with 7 or more incontinent episodes per week at baseline achieved an average 68% reduction in accidents (standard deviation 33 percentage points) and a median of 77%. The distribution is very skewed and increases to its theoretical maximum at 100%. Because of the skewness and the absence of a right "tail" it is assumed that a nonparametric Wilcoxon rank sum test will be used for the primary analysis.

A sample size formula from Noether (1987) was used to calculate the sample size required for the Wilcoxon rank sum test with two-sided Type I error α and power 1-β:

$$N = (Z_{1-\alpha/2}+Z_{1-\beta})^2 / 3(\theta-.5)^2,$$

where Z_c is the c^{th} percentile from a standard normal distribution and θ is the probability that a randomly selected observation from one group is larger than a randomly selected observation from the other group. To calculate θ, it was noted that the distribution of the percent reduction in incontinent episodes can be approximated by an exponential distribution after making a simple transformation. In particular, denoting the percent reduction by R, then S=100-R very closely follows an exponential distribution. Now, for two independent exponential distributions, S_1 and S_2, with rate parameters λ_1 and λ_2 respectively, the probability that a randomly selected observation from S_1 is greater than a randomly selected observation from S_2 is $\theta = Pr(S_1>S_2) = \lambda_2/(\lambda_1+\lambda_2)$.

Using the above formulas, if the true median percent reduction in incontinent episodes are 75% and 85% with drug and combined therapy, then the sample size required to detect a difference with 85% power is 192 (96 per group). If the medians are 80% and 90%, then 108 (54 per group) would be required. Therefore, the sample size required for the primary endpoint of successful discontinuation of drug should be sufficient for this "percentage reduction" endpoint.

C.8.3 Interim Data Monitoring

Formal interim data monitoring will focus on comparing the randomized treatment groups with respect to the primary endpoint. Since the primary endpoint for a particular patient can take as much as 8 months after randomization to determine, this delay must be considered in scheduling the interim analyses. Interim analyses will be conducted when approximately one third and two thirds of patients have reached 8 months after randomization. The methodology of Lan and DeMets will be used to implement an O'Brien-Fleming stopping rule (Lan, 1983; O'Brien, 1979). The Lan and DeMets methodology allows flexibility in the precise timing of the interim analyses. For example, if at the second scheduled interim analysis, data from 70% (instead of 67%) of patients are available, the stopping boundary can be adjusted accordingly. Table 2 shows the p-value cutoffs assuming two interim analyses at 33% and 67% of total information, and the final analysis at 100% of total information.

Table 2. O'Brien-Fleming stopping boundary with three equally spaced analyses. A p-value less than the p-value cutoff shown indicates that the stopping boundary has been crossed.

N	% of Total Information	P-Value Cutoff
100	33%	.0002
200	67%	.0121
300	100%	.05

In addition, treatment differences for any endpoint (including the primary endpoint) that are significant at the .001 level will be brought to the attention of the DSMB for consideration of possible early stopping. However, the intent of the stopping rule is that it should be considered a guideline and not a hard-and-fast rule. Instead, the evidence should be considered in the context of other study data. Accordingly, DSMB reports will ordinarily include summaries of a variety of study endpoints, patient characteristics, adverse events, data quality, and any unanticipated problems that arise during the conduct of the trial.

C.8.4 Analytic Approach

a. Treatment Effects

The primary analysis of the primary endpoint will use Fisher's Exact test to compare success rates between the two treatment groups, according to the intention-to-treat principal. Thus, for example, patients randomized to combined drug plus behavioral treatment will be analyzed in that group even if they are non-compliant with the behavioral treatment. Patients without documentation of a success (e.g., patients who drop out of the study or who do not return a bladder diary) will be considered failures in the primary analysis. Secondary analyses will be conducted to evaluate treatment comparisons according to treatment received and among protocol-compliant patients.

A variety of analyses will be conducted in secondary analyses. The percentage reduction in incontinent accidents will be calculated from baseline to Week 10, from baseline to Month 8 and from Week 10 to Month 8. Because of the expected skewed distributions, these measures will be analyzed with descriptive statistics and the Wilcoxon rank-sum test. Similar analyses will be conducted for percentage reduction in total voids, and for fluid intake volume-adjusted changes in accidents and voids. Resumption of anti-incontinence medications will be analyzed with time-to-event methods, transforming the Week 10 visit to "time 0". This will allow an assessment of the percentage of patients who remain off drug for various lengths of time. Patients who never discontinue medications will be given a time of 0 and those who never resume medications will be censored at the end of follow-up.

Treatment comparisons will be conducted controlling for randomization strata: patients reporting <14 and ≥ 14 incontinent accidents per week at baseline, and patients with and without any self-reported stress symptoms on the MESA at the "rarely" frequency level or greater. Covariate-by-treatment interaction tests will be used to assess whether the treatment comparisons differ across subgroups (Assmann, 2001).

b. Cost Analyses

The objectives of the costs analyses are to:

1. estimate direct and indirect costs of routine care and treatment for urge urinary incontinence;
2. quantify women's preferences (utilities) for incontinence health states and willingness-to-pay for improvement in incontinence;
3. evaluate the effect of drug therapy alone and drug therapy combined with behavioral treatment on costs, utilities, and willingness to pay for improvement in incontinence; and
4. perform cost-utility and cost-benefit analyses of drug therapy alone and drug therapy combined with behavioral treatment for urge urinary incontinence.

The analytical approach for each objective is as follows.

1) Cost Estimates Mean direct and indirect costs of urge urinary incontinence with 95% confidence intervals will be calculated from baseline data. The association of costs and incontinence severity (number of incontinence episodes recorded on the 7-day bladder diary, pad test) will be examined using multiple linear regression models, provided a suitable normalizing transformation of the cost outcome can be found; otherwise proportional odds models will be used to analyze an ordinal transformation. The shape of the cost/severity association will be examined using standard methods for detecting non-

linearities, including categorical transformations of the severity variable and nonparametric smoothing. Multiple regression methods will be used to examine possible confounding, modification, and mediation of the associations between UI severity and cost by covariables including age, annual income, employment status, and condition-specific QOL (IIQ, UDI).

2) Preferences and Willingness to Pay Mean utilities and willingness-to-pay for improvement in incontinence and 95% confidence intervals will be calculated from baseline data. By convention, utility is measured on a 0.0 to 1.0 scale in which 0.0 is the least desirable state, generally but not always associated with death, and 1.0 is the most desirable state, associated with perfect health. States of health between death and perfect health are then quantified in relation to these extreme states. Willingness to pay will be evaluated as an absolute dollar amount and as a percent of each participant's income. The association of both utilities and willingness-to-pay and incontinence severity (number of incontinence episodes recorded on the 7-day bladder diary, pad test) will be examined using methods outlined for Objective1.

3) Treatment Effects on Costs The effects of treatment type on changes in costs, utilities, and willingness to pay for improvement in incontinence will be evaluated by comparing the randomized groups. Results will be summarized using means and quantiles (median, quartiles, range) of the changes, as well as the underlying data at baseline and end of study. The Wilcoxon rank sum test will be used to assess statististical significance, because adjustment of the randomized comparison should not be necessary, and transformations of the outcomes can thus be avoided. If substantial between-group imbalances are found by the data coordinating center, adjusted regression analyses using suitably transformed outcomes will be considered.

In supplementary analysis, nested regression models will be used toexamine mediation of the effects of treatment type on these three change outcomes by overall treatment success and treatment success specific to urge incontinence. In this analysis, attenuation of the coefficient for treatment type after addition of the treatment success indicators to the model would indicate mediation. Confidence intervals for the relative change in the regression coefficient will be constructed using an adaptation of the methods of Freedman for logistic regression (Freedman et al, 1992). Additional exploratory analysis will be carried out among women who do not achieve treatment success to examine the associations between their post-treatment incontinence severity, change since baseline in severity, and changes in costs, utilities, and willingness to pay.

In addition, multiple regression analysis will be used to identify independent predictors of changes in costs, utilities, and willingness to pay. Since treatment success is likely to be the primary predictor of these outcomes, this analysis will be guided by data coordinating center findings on predictors of treatment success. Interactions between other predictors and surgery type will also be considered.

4) Cost Utility and Cost Benefit Cost-utility and cost-benefit analyses will be performed to compare strategies of no intervention (assumptions will be based on baseline data collected in the UITN and participants will be assumed to remain in the same state of health throughout the modeling timeframe), drug therapy alone and drug therapy combined with behavioral treatment. -The economic evaluation will estimate net cost per treatment success in each arm of the model (no intervention, drug alone, drug and behavioral therapy) and marginal cost per treatment success and per quality adjusted life year (QALY) between the groups.

Generalizable costs will be used as described in sections C.5.2(f). Cost of routine care (Objective 1) and utilities derived in this study (Objective 2) will be used. This analysis will adhere to guidelines published by the Panel on Cost-Effectiveness in Health and Medicine convened by the United States Public Health Service (Gold, 1996). In addition, a cost-benefit analysis will be performed that values both health outcomes and costs of medical interventions in dollars. Health outcomes will be converted into monetary values using the willingness to pay method (Objective 2). For a chronic condition like incontinence with minimal associated morbidity and mortality but high impact on quality of life, cost-benefit analysis may be a very appropriate method to assess patient's preferences for incontinence severity, quality of life and treatment trade-offs.

DATA 3.0 decision analysis (or equivalent) software will be used. The influence of alternate management approaches and other estimates that would influence the results of this analysis will be assessed in the course of sensitivity analyses. Univariate sensitivity analyses will be performed on all variables used in the baseline analyses, including probabilities, utilities, and costs, to test the robustness of the outcomes of these analyses to alternative assumptions regarding input variables. A Monte Carlo simulation will be used to vary all of these input parameters over their relevant ranges simultaneously and be used to estimate the 95% confidence intervals of our incremental analyses.

REFERENCES

Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000; 355:1064-1069.

Baigis-Smith J, Smith DAJ, Rose M, Newman DK. (1989). Managing urinary incontinence in community-residing elderly patients. The Gerontologist, 29:229-233.

Bowden, A., Colman, S., Sabounjian, L., Sandage, B., Schwiderski, U., Zayed, H. (2003). Psychometric validation of an urgency severity scale (IUSS) for patients with overactive bladder. International Continence Society, Abstract #119.

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

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

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

Burgio KL, Goode PS, Locher JL, Umlauf MG, Roth DL, Richter HE, Varner RE, Lloyd LK. (2002). Behavioral training with and without biofeedback in the treatment of urge incontinence of older women. A randomized controlled trial. JAMA; 288:2293-2299.

Burgio KL, Locher JL, Goode PS et al. (1998). Behavior vs drug treatment for urge urinary incontinence in older women. JAMA, 280:1995-2000.

Burgio KL, Locher JL, Goode PS. (2000). Combined behavioral and drug therapy of urge incontinence in older women. J Am Ger Soc, 48:370-374.

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

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

Burgio KL, Whitehead WE, Engel BT. (1985). Urinary incontinence in the elderly: Bladder-sphincter biofeedback and toileting skills training. Ann Intern Med, 104:507-515.

Burton JR, Pearce KL, Burgio KL et al. (1988). Behvioral training for urinary in ontinence in elderly ambulatory patients. J Am Ger Soc, 36: 693-698.

Cardinale, V, ed. Drug Topics: Red Book.. 1997, Medical Economics Co, Inc: Montvale, NJ.

Coyne, K. A Summary of the Validation of the OAB-q: A Disease-Specific Overactive Bladder Questionnaire. Unpublished Report for Pharmacia Corporation, (May 15, 2002) Bethesda MD: MEDTAP International, Inc.

Dowell, C.J., et al., Calculating the direct costs of urinary incontinence: a new test instrument. BJU International, 1999. 83(6): p. 596-606.

Elkadry EA, Kenton, KS, FitzGerald MP, Schott, S, Brubaker, L. (2003) Patient-selected goals: A new perspective on surgical outcome. Am J Obstet Gynecol, 189(6): 1551.

Fantl, J., et al., (1995) Urinary incontinence in adults: acute and chronic management. Clinical Practice Feeny, D., et al., Multi-attribute health status classification systems. Health Utilities Index. Pharmacoeconomics, 7(6): p. 490-502.

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

Freedman, L.S., B.I. Graubard, and A. Schatzkin, Statistical validation of endpoints for chronic diseases. Stat Med, 1992. 11: p. 167-78.

Furlong, W., et al., Multiplicative multi-attribute utility function for the health utilities index mark 3 (HUI3) system: a technical report. 1998, McMaster University Centre for Health Economics and Policy Analysis.

Gold, M.R., Cost-effectiveness in health and medicine. 1996, New York: Oxford University Press. xxiii, 425.

Goode PS, Burgio KL, Locher JL et al. (2002). Urodynamic changes associated with behavioral and drug treatment of urge incontinence in older women. J Am Ger Soc, 50:808-816.

HealthCare Consultants of America, I., 2000 Physicians Fee & Coding Guide. 2000, Augusta, GA: HealthCare Consultants of America, Inc.

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

Hollenberg, J.P., et al., Cost-effectiveness of splenectomy versus intravenous gamma globulin in treatment of chronic immune thrombocytopenia in childhood. J Peds, 1988. 112:530-539.

Hunskaar, S., & Vinsnes, A. (1991). The quality of life in women with urinary incontinence as measured by the sickness impact profile. JAGS, 39, 378-382.Jarvellin M, Vikevainen-Tervconen L, Moilanen J, Huttennen Nn. Enuresis in seven year old children. Acta Paedriatr Scand 1988; 77:148.

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

Kobelt, G., Economic considerations and outcome measurement in urge incontinence. Urology, 1997. 50(6A Suppl): p. 100-7; discussion 108-10.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70:659-663.

Mattiasson A, Blaakaer J, Hoye K, Wein AJ, and the Tolterodine Scandinavian Study Group. Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. BJU International, 2003. 91:54-60.

McClish, D.K., et al., Use and costs of incontinence pads in female study volunteers. Continence Program for Women Research Group [see comments]. J Wound Ostomy Contin Nurs, 1999. 26: p. 207-8, 210-3.

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

Mittmann, N., et al., Utility scores for chronic conditions in a community-dwelling population. Pharmacoeconomics, 1999. 15(4): p. 369-76.

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

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

Noether GE. Sample size determination for some common nonparametric tests. J Am Statist Assoc 1987; 82:645-647.

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

O'Brien, B.J., et al., Cost-Effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin: a Canadian perspective. Clin Ther, 2001. 23(12): p. 2038-49.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.

Ouslander, J. and R. Kane, The cost of urinary incontinence in nursing homes. Med Care, 1983. 22: p. 69-79.

Ramsey, S., T. Wagner, and T. Bavendam, Estimated costs of treating stress urinary incontinence in elderly women according to the AHCPR clinical practice guidelines. The American Journal of Managed Care, 1996. 2(2): p. 147-154.

Rittig. S. Nocturnal enuresis at the molecular level. Scand J Urol Nephrol Supple 1995;173:15.

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

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

Sowell, V. and e. al., A cost comparison of five methods of managing urinary incontinence. Quality Review Bulletin, 1987. 13: p. 411-14.

Steinhausen H, Gobel D. Enuresis in child psychiatric clinic patients. J Am Acad Child Adolesc Psych 1989;28:279.

Subak, L.L. and A.B. Caughey, Measuring cost-effectiveness of surgical procedure. Clin Obstet Gynecol, 2000. 43: p. 551-60.

Subak, L.L., A.B. Caughey, and A.E. Washington, Cost-effectiveness analyses in *Obstetrics and Gynecology*: evaluation of methodological quality and trends. J Reprod Med, 2002. 47: p. 631-9.

Subak, L.L., et al., Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol, 2001. 98: p. 646-51.

Subak, L.L., et al., The effect of behavioral therapy on urinary incontinence: a randomized, controlled trial. Obstet Gynecol, 2002. 100: p. 72-8.

Thomas, T. M., Plymat, K. R., Blannin, J., & Verbugge, L. (1980). Health diaries. Medical Care, 18, 73-95.

Wagner, T.H. and T.W. Hu, Economic costs of urinary incontinence in 1995. Urology, 1998. 51(3): p. 355-61.

Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. Medical Care 1996; 34: 220-233.

Wilson, L., et al., Annual costs of urinary incontinence. Obstet Gynecol, 2001. 98: p. 398-406.

Wyman, J., The 'costs' of urinary incontinence. European Urology, 1997. 32 Suppl 2: p. 13-9.

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

APPENDIX A: SCHEDULE OF TREATMENTS AND MEASUREMENTS

		WEEK 0				WEEK 10	MONTH 4	MONTH 6	MONTH 8	MONTHS 14, 20, 26
	VISIT 0	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISITS 9-11
	Baseline Assessment	RANDOMIZATION & INTERVENTION VISIT 1	INTERVENTION VISIT 2	INTERVENTION VISIT 3	INTERVENTION VISIT 4	IN-PERSON VISIT: END STAGE 1	IN-PERSON OR TELEPHONE VISIT	TELEPHONE VISIT	IN-PERSON VISIT: END STAGE 2	LONG-TERM FOLLOW-UP
History	X					X			X	X
Med Audit	X	X	X	X	X	X	X	X	X	X
MESA	X									
UCSF	X									
PE	X									
PFMA	X					X			X	
POP-Q	X					X			X	
PVR	X									
7-Day Diary	X		X	X	X	X	X	X	X	X
IIQ	X					X	X	X	X	X
UDI	X					X	X	X	X	X
OAB-q	X					X	X	X	X	X
SF-12	X					X	X	X	X	X
HUI3	X					X	X	X	X	X
IE	X					X	X	X	X	X
WTP	X					X	X	X	X	X
PSQ						X	X	X	X	X
SEP	X	X	X	X	X	X	X	X	X	X
*Adherence			X	X	X	X	X	X	X	X
UI Tx Status						X	X	X	X	X
Urinalysis	X									

Key: IE: Incontinence Expenses; PE: Physical examination; PFMA: Pelvic floor muscle assessment (i.e. Brinks); PSQ: Patient satisfaction questionnaire; SEP: Side effect profile (i.e. Symptoms Checklist); WTP: Willingness to pay

*Adherence during Intervention Visits includes pelvic floor assessments for those in the combination treatment arm.

APPENDIX B: COMBINATION TREATMENT PROTOCOL

The Combination Treatment Protocol
Drug Therapy Plus Behavioral Treatment

Overview

Combined drug therapy plus behavioral treatment (hereafter called Combination Treatment) will be conducted in 4 visits separated by two to three week intervals, over a period of not more than 10 weeks. Patients will receive both standard drug therapy and behavioral treatment. Behavioral training in the clinic will be supplemented with verbal and written instructions for home practice to be conducted daily between visits. The drug-intervention component of each intervention visit is the same in both treatment arms.

Treatment activities included in the combination treatment arm will be specified to establish a Network-wide standard that will provide BE-DRI staff with clear guidelines for all intervention activities. This standardization will ensure that the intervention is provided in the same manner to all patients both within and across clinical centers.

The objective for each combination treatment visit is threefold:

- Deliver the basic elements of **standard care drug treatment** including drug distribution; evaluation of adherence with the prescribed drug regimen; and assessment and treatment of side effects (symptoms) that may be related to use of Detrol LA.
- Deliver the basic elements of **behavioral training** including pelvic floor muscle training and practice; teaching urge suppression and urge avoidance strategies; bladder training; evaluation of adherence with the behavioral strategies and exercise regimen; identification of barriers to adherence; and advice about how to overcome them.
- Maximize accuracy in completion of **bladder diary** documentation. All patients will be instructed to complete bladder diaries throughout the intervention period. Since a 7-day bladder diary is used as the primary outcome measure, accuracy in record keeping is essential to achieve the aims of the BE-DRI Trial. The Interventionist will conduct reviews of the completed diaries to check diaries for legibility, validity and completeness.

Standard Drug Therapy

The drug therapy selected for use in the BE-DRI trial is a 4mg daily dose of tolterodine tartrate extended release capsule, trade name Detrol LA. During the 10-week intervention period, one break from drug treatment of ≤7 days is allowable, recognizing that such a break might be clinically indicated; e.g. during treatment of another illness. Some patients may report bothersome side effects during or between study visits. Uniform interventions have been developed for the common side effects of dry mouth and constipation. All other bothersome side effects will be treated at the discretion of the Interventionist in accordance with her customary clinical practice. The daily dose of Detrol LA may be decreased to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level. Detrol LA may be discontinued at the discretion of the Interventionist if the patient continues to suffer from intolerable side effects, although the need to discontinue drug therapy altogether should be uncommon. In a Phase 3 controlled clinical trial, Pfizer found treatment with Detrol LA 4mg daily was discontinued due to adverse events in 2.4% of patients taking Detrol LA. (http://www.pfizer.com/download/uspi_detrol_la.pdf).

Subsequent study visits should still be conducted per protocol for patients who stop taking Detrol LA.

Combination Treatment Visit 1

Teach Pelvic Floor Muscle Control

At the time patients are randomized and introduced to the Interventionist, they will have completed the 7-day baseline bladder diary and the self-administered Symptoms Checklist, data form number 205 (FM205).

Bladder Diary Review

At the start of the visit, the Interventionist reviews the baseline bladder diary with the patient, noting the time, size, circumstances and type of each accident. The weekly frequency of incontinence is calculated and shared with the patient. The Interventionist also calculates the 24-hour voiding frequency (mean of 7 days) in order to identify patients who have more than 8 voids per 24 hours (trigger for bladder training). In addition, the Interventionist reviews the voided volumes and calculates the total 24-hour voided volume (mean of the 2-day voided volume diary) in order to identify patients who void greater than 70 oz. per day (trigger for fluid management counseling). The Interventionist also reviews the diary for completeness, to be certain all essential elements are included and all the patient's recordings are legible and codable. Interventionists should also reinforce and/or remind the patient about the proper methods of completing the bladder diary accurately as needed. Refer to the Bladder Diary Procedures for a description of elements required for a complete Diary.

Standard Drug Therapy

Prescribing and Dispensing Detrol LA

Detrol LA 4 mg daily, is prescribed during the baseline study visit (Visit 0), and patients are given a 30-day supply of Detrol LA at the first intervention visit (Visit 1). Each clinical center will make arrangements for the dispensing of Detrol LA in accordance with their center's institutional policies pertaining to the dispensing of prescribed medication. NOTE: *Detrol LA is not an experimental drug.*

Standard Drug Education/Information

A Detrol LA Information Handout has been developed specifically for the BE-DRI trial and is given to all patients at Visit 1 (Attachment A). The Interventionist delivers the standard study drug education by thoroughly reviewing the handout with the patient

Patients should be instructed to bring their bottle of Detrol LA with them when they return to the center for each of their study visits as an actual pill count must be completed at all subsequent intervention visits to evaluate adherence with drug therapy.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist next reviews all "yes" symptoms on the Symptoms Checklist and initiates treatments or makes recommendations for bothersome symptoms if indicated. If the patient complains of problems with dry mouth or constipation, standardized advice for these complaints will be offered and the information handouts developed for these 2 common complaints are given to the patient (Attachments B and C). Other recommendations/interventions may be offered for all other bothersome symptoms in accordance with the individual Interventionist's standard practice.

Fluid Management

All patients receive the BE-DRI Fluid Management Handout containing general recommendations about fluid intake and output (Attachment D). The average urine output for a healthy adult is considered to be 40 to 50 ounces per day. If the patient's 24-hour voided volume exceeds 70 ounces per day, she is also counseled about normalizing her fluid intake. Recommendations to the patients include consuming no more than 6 to 8 eight-oz. glasses of liquids per day (much of which can be in the form of solid food) and distributing their intake over the day rather than consuming a lot at one time.

Behavioral Training

Teach Pelvic Floor Muscle Control and Exercise

The main focus of this initial session is to assist the patient to identify her pelvic floor muscles and learn how to contract and relax them properly. Pelvic floor muscle training will be conducted using verbal feedback based on vaginal palpation. Patients are taught how to contract and relax the pelvic floor muscles while keeping abdominal muscles relaxed. The goal is to increase intraurethral pressure (by means of contracting pelvic floor muscles) while minimizing intra-abdominal pressure (which contributes to bladder pressure).

Identifying, Isolating and Relaxing the Pelvic Floor Muscles

With the patient in the supine position (with hips and knees flexed), the Interventionist inserts one or two fingers into the vagina and instructs the patient to contract the pelvic floor muscles around the fingers. The following wording is suggested for the Interventionist to help patients find their pelvic floor muscles:

> *"Remember, the pelvic floor muscles start at the pubic bone and go down to the tail bone. We are focusing on the muscles that surround the vagina because it is easier to find the pelvic floor muscles here, but tightening the vagina tightens the muscles all the way up to the front, near the bladder. I am going to insert my fingers into the vagina and I want you to try to squeeze your vaginal muscles around my fingers. As you squeeze, think of pulling my fingers in, toward your head."*

Exercise Block #1. The patient performs up to 5-10 quick muscle contractions (1-second hold, followed by a 2- second rest) depending on fatigue, with the Interventionist providing verbal feedback as needed regarding the patient's performance. If the patient cannot perform contractions via digital vaginal palpation, the Interventionist places a finger just inside the anal opening to encourage muscle contraction during *Exercise Block #2*.

Exercise block #2. After a two-minute rest interval, the patient is asked to perform another 5-10 repetitions of the quick muscle contractions. During this set of contractions, the Interventionist assists her to contract and relax the pelvic floor muscles, while relaxing the buttocks, thigh, and abdominal muscles. The Interventionist can place a hand on the abdomen to detect abdominal muscle tension, and teach the patient to do the same. Suggested wording for the Interventionist:

> *"Keep the abdominal and hip muscles relaxed while you do these exercises. Tensing your abdominal muscles works against bladder control because it can press on the bladder and increase pressure inside the bladder. This pushes urine out, rather than holding urine in. Other muscles we need to keep relaxed are the thighs and buttocks. When you are first learning it takes practice and concentration to isolate the correct muscle, but it will get more automatic with time."*

Tips to help patients relax their abdominal and hip muscles:

- When you isolate the muscle and perform the exercise correctly, no one can tell you are exercising.
- Don't hold your breath while squeezing your muscles.
- Breathe in and out through your mouth.
- Place your hands on your tummy to make sure you are not tightening the wrong muscles.
- Do more moderate squeezes.
- Do not squeeze your buttocks together.
- Your back should not arch.
- Your buttocks should not lift up from the bed.

During this set of 5-10 contractions the Interventionist also emphasizes the importance of relaxing pelvic floor muscles completely between each contraction. The Interventionist uses the following phrases to encourage muscle relaxation:

> *"Contracting your muscles repeatedly will make them stronger, but relaxing the muscles is equally important. Relaxation allows blood and oxygen to get back into the muscles and prepare them for exercising. Allowing the muscles to completely relax between squeezes also helps the muscle to build and "bulk up" faster."*

Evaluation of Exercise Technique

After a two-minute rest interval, the Interventionist asks the patient to perform a final set of 5-10 quick muscle contractions. The purpose of this evaluation is to determine if the patient can correctly perform 5 consecutive contractions. The Interventionist documents whether or not the patient can perform 5 consecutive contractions and whether she can do so without Valsalva or excessive accessory muscle contraction.

Home Exercise Prescription

After training, the Interventionist gives the patient verbal and written instructions for home practice. For each contraction, the Interventionist instructs the patient to tighten her muscles for a maximum of 3-seconds followed by 6-seconds of muscle relaxation. The patient is instructed to perform a total of 45 contractions every day, divided into manageable sessions, usually 3 sessions of 15 exercises each. They are advised to perform one session in the supine (lying) position and two sessions sitting.

In addition, the Interventionist instructs the patient to integrate the exercises into other daily activities such as standing in line, sitting in a car at a stoplight, washing dishes, or sitting at a desk. A template for the home program is presented in Attachment F. The program can be individualized as needed with regard to the schedule of exercises and duration of contraction and relaxation.

Tips for the Interventionist:

- Remind the patient that this is a new exercise for most people and that she will get better with practice.
- It takes practice to achieve good isolation.
- Encourage persistence.
- Praise patient efforts.

Appointments

An appointment for a return visit in 2 weeks and appointments for *all remaining* intervention visits will be made at this time. An Appointment Log is available for this purpose (See Attachment E).

Ideally, the 4 intervention visits are scheduled evenly throughout the 10-week intervention period. The following table provides a guide for scheduling the visits.

Visit Target Days:	Visit 2: Treatment Day 14
	Visit 3: Treatment Day 28
	Visit 4: Treatment Day 49
	Visit 5: Treatment Day 70

Use this table as a guide when scheduling the visits. Some leeway is allowed for extenuating circumstances, but every effort should be made to keep the patient on a strict schedule for the intervention visits. Details about the limits of compressing or stretching the required study visit windows are described elsewhere.

Note: the shorter, 2-week time interval between the earlier visits is intended to allow better management in the earlier weeks; the window following Visits 3 and 4 increases to 3 weeks. Following this guideline will permit visit scheduling on the same weekday throughout the intervention period, which will likely be a convenience for most patients.

Patient Materials

Patients are sent home with:

- 30-day supply of Detrol LA 4mg
- Detrol LA Information Handout (Attachment A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Fluid Management Handout (Attachment D)
- Pelvic Floor Muscle Exercise Prescription (Attachment F)
- Appointment Log (Attachment E)
- Bladder Diaries, enough to complete continuously between visits. The interventionist encourages accuracy and consistency in completing the diaries.

Documentation

All critical activities and measurements completed at Visit 1 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 1. (FM211).

Combination Treatment Visit 2
Teach Behavioral Strategies

Symptoms Checklist and Exercise Questionnaire

The patient should complete the Symptoms Checklist (FM205) and the Pelvic Floor Muscle Exercise Questionnaire (FM244) in the waiting area prior to the start of the visit with the Interventionist.

Bladder Diary Review

The Interventionist reviews the bladder diaries with the patient, noting the time, size, circumstances and type of each accident (including stress incontinence). In addition, the weekly frequency of incontinence is calculated and shared with the patient. The Interventionist also notes if the 24-hour voiding frequency is greater than 8.

The bladder dairies are also reviewed for completeness, legibility and validity at every intervention visit. The Interventionists should be certain that all essential elements are included and all patient recordings are legible and codable. Interventionists should reinforce good record keeping and review proper record keeping for the areas that require improvement.

Medication Audit Update

The Interventionist asks the patient if she has started taking any of the medications listed on the Detrol LA Information Handout, i.e. "need-to-know" medications.

Standard Drug Therapy

Adherence to the Drug Regimen

Next, the Interventionist completes the pill count and interviews the patient to evaluate the level of adherence with the prescribed drug regimen.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist also reviews all "yes" symptoms on the Symptoms Checklist with the patient. Bothersome side effects reported by the patient on the Checklist (FM205) or in conversations with the Interventionist during or between study visits are treated at the discretion of the Interventionist in accordance with her customary clinical practice. Uniform interventions developed for the common side effects of dry mouth and constipation should be used for these complaints (Attachments B and C).

Decreasing the dose or discontinuation of Detrol LA

The daily dose of Detrol LA may be decreased to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level to the patient. Detrol LA may be discontinued at the discretion of the Interventionist if the patient continues to suffer from intolerable side effects but every effort should be made to help the patient continue on the medications.

Subsequent study visits should still be conducted on schedule for patients who stop taking Detrol LA.

Dispensing Detrol LA

The initial 30-day supply of Detrol LA dispensed at Visit 1 should be sufficient to last until Visit 3. If for any reason the Interventionist believes this supply will be inadequate to cover the days until the next study visit, patients will be provided with another 30-day supply of Detrol LA at Visit 2.

If the Detrol LA dose is decreased to 2mg, a 30-day supply of the Detrol LA 2mg capsules will be dispensed. Any remaining 4 mg capsules must be returned to the Interventionist. Likewise, if Detrol LA is discontinued altogether, all remaining capsules should be returned to the Interventionist.

Behavioral Training

Exercise Adherence

Next, the Interventionist reviews the patient's Exercise Questionnaire (FM244), which includes questions about adherence and barriers to exercise. She discusses any problems that are identified and offers suggestions to improve compliance (Appendix G).

Evaluation of Exercise Technique

The Interventionist then evaluates the patient's ability to perform the maximal three-second contraction. Using digital vaginal palpation, she asks the patient to demonstrate her exercises with 3-second contractions and 6-second relaxations. The Interventionist documents whether the patient is able to perform 5 contractions and whether she is able to do so without Valsalva or excessive accessory muscle contraction.

Home Exercise Prescription

The Interventionist instructs the patient to increase the duration of pelvic floor muscle contractions up to 6 seconds and relaxation time to 12 seconds for each exercise repetition. The patient is instructed to continue 45 total contractions per day. The position for exercise is progressed at this visit to 15 contractions in supine, 15 contractions in sitting, and 15 contractions in standing.

Teach Urge Suppression

The focus of Visit 2 is on teaching patients behavioral strategies. The primary strategy is urge suppression, including how to respond adaptively to the sensation of urgency and techniques to avoid urine loss and manage urgency. In addition to strengthening the pelvic floor muscles it is important to use them actively to prevent incontinent episodes. Patients with urge incontinence typically report that they rush to the toilet when they experience a sensation of urgency to void. They are instructed not to rush to the toilet because this movement increases intra-abdominal pressure on the bladder, increasing the likelihood of incontinence. They are also taught that rushing *to the toilet* in particular is counterproductive, because it places her in the presence of cues that have been conditioned to trigger detrusor contraction/incontinence. Patients are taught a more effective pattern of responding to urgency. Instead, of rushing to the toilet, they are encouraged to pause, to sit down if possible, to practice relaxing, and to contract the pelvic floor muscles several times in an effort to diminish urgency, inhibit detrusor contraction, and prevent urine loss. When urgency subsides, they should then proceed at a normal pace to the toilet. If the urge returns on the way to the toilet, the patient should stand still and repeat pelvic floor muscle contractions until the urge is again suppressed, then proceed at a normal pace to the toilet.

Bladder Training

Patients who void >8 times per day are also started on a form of bladder training to increase their voiding interval. Once they have achieved the ability to suppress an urge and then walk (not rush) to the toilet, they are encouraged to expand their voiding interval. Instead of walking to the toilet immediately after suppressing the urge, they are encouraged to delay voiding for 10 minutes. The delay time is then increased incrementally with the goal of voiding every 3 to 4 hours during the day.

Stress Strategies

If the patient also has stress incontinence, the Interventionist teaches "stress strategies," active use of pelvic floor muscle contraction to prevent stress incontinence. First, the bladder diary is reviewed to help the patient identify all circumstances that precipitated stress incontinence in the previous 2 weeks. Then the patient is told that, to avoid these accidents it is important not only to have strong muscles, but also to use them consciously during these circumstances. She is encouraged to attend to these circumstances and to contract her muscles just before and during these circumstances, to keep the urethra closed and prevent urine loss.

Fluid Management

If the patient is on the fluid management regimen, the Interventionist inquires about her fluid intake since the last visit. Any reduction of intake is reinforced and the patient is encouraged to continue reducing fluids to the recommended equivalent of 6 to 8 eight-oz glasses per day.

Appointments

At the close of the visit, the Interventionists should review and confirm dates and times for all subsequent intervention visits. The Appointment Log should be used for this review and corrected if appointment times and/or dates are changed.

The Interventionist should also contact the Study Nurse/Interviewer to confirm the patient's appointment day and time for Visit 5.

Patient Materials

Patients are sent home with:

- Sufficient supply of Detrol LA
- Detrol LA Information Handout as needed (Attachments A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Handout of Urge Suppression Strategy (Attachment J)
- Handout of Urge Suppression Strategy for patients in Bladder Training (Attachment K)
- Stress Strategies Handout as needed (Attachment L)
- Pelvic floor muscle exercise prescription (Attachment F)
- Appointment Log (Attachment E)
- Bladder Diaries: enough to complete continuously between visits. The Interventionist encourages accuracy and consistency in completing the diaries.

Documentation

All critical activities and measurements completed at Visit 2 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 2. (FM222).

If the Interventionist has contact with the patient between Visit 1 and Visit 2, a record of the contact including any measurements or interventions completed should be recorded in real time in a medical record or other source document. Selected data will also be abstracted onto the Intervention Data Form for Visit 2. (FM222).

Combination Treatment Visit 3
Reinforce Behavioral Strategies

The focus of Visit 3 is to reinforce the behavioral program and problem-solve with the patient after she has been trying the behavioral strategies to manage urgency and postpone voiding.

Symptoms Checklist and Exercise Questionnaire

The patient should complete the Symptoms Checklist (FM 205) and the Exercise Questionnaire (FM244) in the waiting room prior to seeing the Interventionist.

Bladder Diary Review

The Interventionist again reviews the bladder diaries with the patient, noting the time, size, circumstances and type of each accident (including stress incontinence). The weekly frequency of incontinence is calculated and shared with the patient. The Interventionist also notes if the 24-hour voiding frequency is greater than 8. For patients on the Bladder Training Regimen, the daily frequency of voiding is also calculated and shared with the patient.

The bladder dairies are also reviewed for legibility, completeness, legibility and validity. The Interventionist should be certain that all essential elements are included and all patient recordings are legible and codable. Interventionist should reinforce good record keeping and review proper record keeping for any areas that require improvement.

Medication Audit Update

The Interventionist asks the patient if she has started taking any of the medications listed on the Detrol LA Information Handout, i.e. "need-to-know" medications.

Standard Drug Therapy

Adherence to the Drug Regimen

The Interventionist next completes the pill count and interviews the patient to evaluate the level of adherence with the prescribed drug regimen.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist again reviews any "yes" symptoms on the Checklist and treats bothersome side effects as needed using the uniform interventions for complaints of dry mouth and constipation (Attachments B and C). All other bothersome symptoms are treated at the discretion of the Interventionist in accordance with her customary clinical practice.

Decreasing the dose or discontinuation of Detrol LA

As previously described, Detrol LA may be decreased from 4mg to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level to the patient. And Detrol LA may be discontinued if the patient continues to suffer from intolerable side effects.

Subsequent study visit should still be conducted on schedule for patients who stop taking Detrol LA.

Dispensing Detrol LA

Another 30-day supply of Detrol LA will be dispensed at Visit 3 if a second bottle of 30 capsules was not dispensed at Visit 2. If for any reason the Interventionist believes this supply will be inadequate to cover the days until the next study visit, patients will be provided with a sufficient supply of Detrol LA to last through Day 70, i.e. end of Stage 1

If the Detrol LA dose is decreased to 2mg, a 30-day supply of the Detrol LA 2mg capsules will be dispensed.

Any remaining 4 mg capsules must be returned to the Interventionist. Likewise, if Detrol LA is discontinued altogether, all remaining capsules should be returned to the Interventionist.

Behavioral Training

Behavioral Strategy Adherence and Advice

The Interventionist administers the Behavioral Strategy Problem Checklist (Attachment H). The focus is on problems the patient has encountered using urge suppression strategies or bladder training. These problems are discussed also using the bladder diary, and suggestions given for improving skills and compliance. The Interventionist specifically asks whether the patient has used the urge suppression strategy and how well it worked. In reviewing the patient's efforts to suppress urge and prevent incontinence, the Interventionist offers suggestions for how to manage specific situations that are discovered in the bladder diaries. For example, if the patient is too worried about having an accident to take the risk of using the urge suppression strategy, she might be encouraged to practice the techniques only at home for a time. This may allow her to experience some success with the techniques in a safe environment and gain confidence to try them in other settings.

Bladder Training

If the patient is on the Bladder Training Regimen, the Interventionist inquires about her progress in postponing urination and reviews the bladder diary with the patient. Problems are identified and advice is given for increasing the voiding interval. A new expanded interval is negotiated with the patient and instructions written for home practice.

Stress Strategies

If the patient also has stress accidents, the interventionist inquires about her success using the stress strategies and reviews the bladder diary for any stress accident circumstances. The Interventionist specifically asks whether the patient has used the stress strategy and how well it worked. In reviewing the patient's efforts to prevent stress incontinence, the Interventionist offers suggestions for how to manage specific situations that are discovered in the bladder diaries. For example, if the patient had a stress accident when she forgot to tighten her muscles to brace for a cough or sneeze, she might be encouraged to practice squeeze anyway even if it is too late for that episode. This can strengthen the habit of using pelvic floor muscles and may help her learn to tighten *before* the cough or sneeze the next time it happens.

Fluid Management

If the patient is on the fluid management regimen, the Interventionist inquires about her fluid intake since the last visit. Any reduction of intake is reinforced and the patient is encouraged to continue reducing fluids to the recommended equivalent of 6 to 8 eight-oz glasses per day.

Exercise Adherence

The Interventionist reviews the patient's Exercise Questionnaire, discusses the problems identified, and offers suggestions to improve compliance.

Evaluation of Exercise Technique

The Interventionist evaluates the patient's ability to perform the maximal 6-second contraction. Using digital vaginal palpation, she asks the patient to demonstrate her exercises with 6-second contractions followed by 12-second relaxations. She documents whether the patient is able to perform 5 contractions and whether she can do this without Valsalva or excessive accessory muscle contraction.

Home Exercise Prescription

The Interventionist instructs the patient to increase the duration of pelvic floor muscle contractions up to 8 seconds and relaxation time is increased to 16 seconds for each exercise repetition. The patient is instructed to continue 45 total contractions per day, 15 contractions in each of the 3 positions.

Appointments

The Interventionist should review and confirm dates and times for Visit 4. The Appointment Log should be used for this review and corrected if appointment times or dates are changed.

Patient Materials

Patients are sent home with:

- Sufficient supply of Detrol LA
- Detrol LA Information Handout as needed (Attachments A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Pelvic Floor Muscle Exercise Prescription (Attachment F)
- Behavioral Strategy Instructions
- Handout of Urge Suppression Strategy for patients in Bladder Training (Attachment K)
- Stress Strategies Handout as needed (Attachment L)
- Appointment Log (Attachment E)
- Bladder Diaries: enough to complete continuously between visits. The Interventionist encourages accuracy and consistency in completing the diaries.

Documentation

All critical activities and measurements completed at Visit 3 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 3. (FM233).

If the Interventionist has contact with the patient between Visit 2 and Visit 3, a record of the contact including any measurements or interventions completed should be recorded in real time in a medical record or other source document. Selected data will also be abstracted onto the Data Form for Visit 3. (FM233).

Combination Treatment Visit 4
Reinforce Behavioral Strategies

The focus of Visit 4 is to continue to reinforce the behavioral program and problem-solve with the patient to use behavioral strategies to manage urgency and postpone voiding.

Symptoms Checklist and Exercise Questionnaire

The patient should complete the Symptoms Checklist (FM205) and the Exercise Questionnaire (FM 244) in the waiting area prior to seeing the Interventionist.

Bladder Diary Review

Once again, the Interventionist reviews the bladder diaries with the patient, noting the time, size, circumstances and type of each accident (including stress incontinence). The weekly frequency of incontinence is calculated and shared with the patient. For patients on the Bladder Training Regimen, the daily frequency of voiding is also calculated and shared with the patient.

The bladder dairies are also reviewed for completeness and legibility. The Interventionist should review the diary to be certain that all essential elements are included and all patient recordings are legible and codable. Interventionists should reinforce good record keeping and review proper record keeping for any areas that require improvement.

Medication Audit Update

The Interventionist asks the patient if she has started taking any of the medications listed on the Detrol LA Information Handout, i.e. "need-to-know" medications.

Standard Drug Therapy

Adherence to the Drug Regimen

The Interventionist next completes the pill count and interviews the patient to evaluate the level of adherence with the prescribed drug regimen.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist again reviews any "yes" symptoms on the Checklist and treats bothersome side effects as needed using the uniform interventions for complaints of dry mouth and constipation (Attachments B and C). All other bothersome symptoms are treated at the discretion of the Interventionist in accordance with her customary clinical practice.

Decreasing the dose or discontinuation of Detrol LA

As described in Visit 2, Detrol LA may be decreased from 4mg to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level. And Detrol LA may be discontinued if the patient continues to suffer from intolerable side effects.

Subsequent study visits should still be conducted on schedule for patients who stop taking Detrol LA.

Dispensing Detrol LA

At this last intervention visit, the Interventionist dispenses only the exact amount of Detrol LA that will be required to permit the patient to continue drug therapy to the end of the intervention period, i.e. Day 70. Count the **exact** number of days remaining between the actual date of study Visit 4 and the actual Day 70 (not necessarily the exact date of Visit 5) and only dispense this **exact** number of capsules. Recover as many capsules as necessary at this visit to be sure the patient only has this exact amount. Patients should not continue drug therapy beyond Day 70 even if they took drug less than 70 days because of a break in therapy earlier in the intervention.

If the Detrol LA dose is decreased to 2mg, dispense the exact number of 2mg capsules that will be required to continue drug therapy to the end of the intervention and recover any remaining 4 mg capsules. Likewise, if Detrol LA is discontinued altogether, all remaining capsules must be returned to the Interventionist at this visit.

The Interventionist also stresses the importance of completing the drug-therapy through the end of Stage 1, i.e. Day 70. If for any reason the patient misses any doses, she should not take Detrol LA beyond Day 70. All remaining capsules should be returned to the Study Nurse at Visit 5. If the patient takes all the capsules, she should return the empty bottle at Visit 5.

Behavioral Training

Behavioral Strategy Adherence and Advice

The Interventionist again administers the Behavioral Strategy Problem Checklist. The focus is on problems the patient has encountered using urge suppression strategies, postponing urination (in the Bladder Training Regimen), or using stress strategies. These problems are discussed using examples in the bladder diary, and suggestions given for improving skills and compliance. The Interventionist specifically asks whether the patient has used the urge suppression strategy and how well it worked. In reviewing the patient's efforts to suppress urge and prevent incontinence, the Interventionist offers suggestions for how to manage specific situations that are discovered in the bladder diaries.

Bladder Training

If the patient is on the Bladder Training Regimen, the Interventionist inquires about her progress in postponing urination and reviews the bladder diary with the patient. Problems are identified and advice is given for increasing the voiding interval. A new expanded interval is negotiated with the patient and instructions written for home practice.

Fluid Management

If the patient is on the fluid management regimen, the Interventionist inquires about her fluid intake since the last visit. Any reduction of intake is reinforced and the patient is encouraged to continue reducing fluids to the recommended equivalent of 6 to 8 eight-oz glasses per day.

Exercise Adherence

The Interventionist reviews the patient's Exercise Questionnaire, discusses the problems identified, and offers suggestions to improve compliance.

Evaluation of Exercise Technique

The Interventionist then evaluates the patient's ability to perform the maximal 8-second contraction. Using digital vaginal palpation, she asks the patient to demonstrate her exercises with 8-second contractions followed by 16-second relaxations. The Interventionist documents whether the patient is able to perform 5 contractions and whether she can do this without Valsalva or excessive accessory muscle contraction.

Home Exercise Prescription

The Interventionist instructs the patient to increase the duration of pelvic floor muscle contractions up to 10 seconds and relaxation time is increased to 20 seconds for each exercise repetition. The patient is instructed to continue 45 total contractions per day, 15 contractions in each of the 3 positions.

Preliminary Discussion of Stage 2 Activities including Maintenance Schedule of Exercises

Patients are also instructed to continue voluntary pelvic floor muscle exercises and behavioral strategies in Stage 2 in order to maintain treatment effect. Because this is the last contact between the interventionist and patient, the interventionist explains the importance and function of the maintenance program that will be given to them at Visit.5

The Interventionist also reminds the patient that Visit 5 marks the end of Stage 1 and the beginning of Stage 2. Details about the Stage 2 activities are reviewed briefly at this time. They will be provided to the patient in a written form at the end of Stage 1. The written details, described in the body of a Thank-You Letter, can be hand delivered to the patient at Visit 5 or they can be mailed to the patient for a receipt date that will coincide with the last day of Stage 1.

The Interventionist also prepares an individualized set of instructions for the patient's maintenance program of behavioral strategies and pelvic floor muscle exercises. The maintenance program will consist of 15 exercises each day at the duration the patient achieved during active treatment. The sheet of instructions is reviewed with the patient at Visit 4 but the instructions will be included with the Thank-You Letter describe above and given to the patient at Visit 5. The Thank You Letter including the Instructions for the maintenance program can be hand delivered to the patient at Visit 5 or they can be mailed to the patient for a receipt date that will coincide with the last day of Stage 1.

Appointments

At the end of Visit 4 the Interventionist confirms the day, date and time of the patient's post-intervention follow-up appointment (Visit 5) with the BE-DRI Interviewer. Ideally, the Interventionist will call the Interviewer to confirm the appointment time and verify or correct the patient's Appointment Log as needed.

Patient Materials

Patients are sent home with:

- Sufficient supply of Detrol LA
- Detrol LA Information Handout as needed (Attachments A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Pelvic floor muscle exercise prescription (Attachment F)
- Behavioral strategy instructions
- Handout of Urge Suppression Strategy for patients in Bladder Training (Attachment K)
- Stress Strategies Handout as needed (Attachment L)
- Evaluation Bladder Diaries*
- Post-treatment visit materials
- Appointment Log (with appointment for their post-treatment visit).

* Only one 7-day diary is needed at Study Visit 5, so Interventionists should instruct patients to complete only one 7-day diary during the last week of the intervention. This diary must be completed while the patient is still on drug therapy. In preparation for Visit 5, the Interventionist reinforces the importance of keeping accurate diaries. Patients are reminded that this 7-day diary is essential for measuring any changes in their continence status before and after the intervention. For this Diary the patient must again complete the intake and output measurements.

Documentation

All critical activities and measurements completed at Visit 4 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 4. (FM233).

If the Interventionist has contact with the patient between Visit 3 and Visit 4, a record of the contact including any measurements or interventions completed should b recorded in real time in a medical record or other source document. Selected data will also be abstracted onto the Data Form for Visit 4. (FM233).

Combination Treatment Patient
Post-Treatment Visit 5: End of Stage 1

Recovery of unused Detrol LA capsules

Because this is the end of Stage 1, the Study Nurse must recover all doses of unused Detrol LA. All remaining capsules must be recovered. If the patient took all the capsules, she should return the empty medication bottle at Visit 5.

Delivery of Written Reminder of Stage 2 Activities

At Visit 5, patients are given the "Thank You" Letter (prepared at the end of Visit 4 by the Interventionist) that officially recognizes the end of Stage 1 and reminds the patient of Stage 2 study activities.

Patients in combination treatment are also given the Maintenance Schedule of Exercises Handout prepared for them by their Interventionist and reviewed at Visit 4. The Maintenance Schedule of Exercises Handout will instruct the patient to continue voluntary pelvic floor muscle exercises and behavioral strategies in order to maintain treatment effects in Stage 2. The instructions on the Maintenance Schedule of Exercises Handout will consist of 15 exercises each day at the duration they have achieved during active treatment.

The "Thank You" Letter and Maintenance Schedule Handout should be prepared at Visit 4, sealed in an envelope addressed to the patient and delivered to her via the BE-DRI Evaluation staff at Visit 5 or it can be mailed directly to her home with a receipt date that will coincide with the end of Stage 1.

Documentation

The Interventionist will be required to complete a data form at the end of the Intervention to document all required intervention activities have been completed. If the Interventionist has contact with the patient between Visit 4 and Visit 5, a record of the contact including any measurements or interventions completed should be recorded in real time in a medical record or other source document. Selected data will also be abstracted onto a BE-DRI Data Form.

ATTACHMENTS FOR THE COMBINATION TREATMENT

ATTACHMENT A

INFORMATION ABOUT DETROL LA

INFORMATION ABOUT DETROL LA

BE-DRI

GENERIC NAME: Tolterodine tartrate

ACTION: Detrol helps urinary incontinence by relaxing the bladder muscles so that you do not feel a strong urge to urinate. Detrol LA is one of the drugs used frequently to treat urge incontinence.

Detrol LA is not an experimental drug.

DOSE: Detrol LA should be taken once a day. It is important to take the drug at the same time each day. We recommend that you take the drug at bedtime. The capsule should be taken by mouth with liquids.

MISSED DOSE: Detrol LA is an extended release capsule. This means that the drug is released over a 24-hour period. Therefore, if you forget to take the capsule, you can take it up to 12 hours after the time you usually take the drug.

SIDE EFFECTS: The most common side effects are dry mouth and constipation.
If you develop dry mouth, the following should be helpful:

- Chew sugar-free gum.
- Suck on sugar-free hard candy.
- Sip water, especially during meals to help swallow food.
- Use fluoride toothpaste to help prevent dental cavities.
- Avoid mouthwashes with alcohol. Try 1-teaspoon salt and 1-teaspoon baking soda in a quart of water as a mouthwash.
- Use an oral lubricant, available over-the-counter located near the toothpastes.

If you develop constipation, please ask the nurse for a list of suggestions.

Other less frequent side effects include headache, abdominal pain, dizziness, indigestion, blurred vision, dry eyes, sleepiness or fatigue. Please let us know if you experience any of these symptoms.

OTHER DRUGS: Due to the nature of the study protocol, if you must take any of the drugs listed on the following pages at the time that you are participating in the BE-DRI Study we need to know. Please call the study nurse before taking the drug.

If you have any questions or concerns, please call:

NAME: _____ **PHONE NUMBER:** _____

Need To Know Drugs Listed Alphabetically by Generic Name First

- Amitriptyline (**Elavil, Endep**)
- Amoxapine (**Asendin**)
- Belladonna alkaloids/Phenobarbital (**Donnatal**)
- Clidinium (**Quarzan**)
- Clomipramine (**Anafranil**)
- Desipramine (**Norpramin**, **Pertofrane**)
- Dicyclomine (**Bentyl**)
- Doxepin (**Adapin**, **Sinequan**)
- Duloxetine (**Cymbalta**)
- Glycopyrrolate Tablets (**Robinul, Robinul Forte**)
- Homatropine (**Homapin**)
- Hyoscyamine (**A-Spas S/L, Anaspaz, Cystospaz, Donnamar, ED-Spaz, Gastrosed, Hyco elixir, Hyosyne, Hysosol, Hyospaz, Levbid, Levsin, Levsinex Timecaps, Levsin/SL, Losamine, M**)
- Hyoscyamine sulfate (**Cystospaz-M**)
- Imipramine (**Janamine**, **Tofranil**)
- Imipramine Pamoate (**Tofranil PM**)
- Mepenzolate (**Cantil**)
- Nortriptyline (**Aventyl**, **Pamelor**)
- Oxybutynin (**Ditropan, Oxytrol patch**)
- Propantheline (**Pro-Banthine**)
- Propantheline Bromide (**Pro-Banthine**)
- Protriptyline (**Vivactil**)
- Tolterodine (**Detrol**)
- Trimipramine (**Surmontil**)

Need To Know Drugs Listed Alphabetically by Trade Name First

- **Adapin** (Doxepin)
- **Anafranil** (Clomipramine)
- **Anaspaz** (Hyoscyamine)
- **Asendin** (Amoxapine)
- **A-Spas S/L** (Hyoscyamine)
- **Aventyl** (Nortriptyline)
- **Bentyl** (Dicyclomine)
- **Cantil** (Mepenzolate)
- **Cymbalta** (Duloxetine)
- **Cystospaz,** (Hyoscyamine)
- **Cystospaz-M** (Hyoscyamine sulfate)
- **Detrol** (Tolterodine)
- **Ditropan** (Oxybutynin)
- **Donnamar** (Hyoscyamine)
- **Donnatal** (Belladonna alkaloids/Phenobarbital)
- **ED-Spaz** (Hyoscyamine)
- **Elavil** (Amitriptyline)
- **Endep** (Amitriptyline)
- **Gastrosed** (Hyoscyamine)
- **Homapin** (Homatropine)
- **Hyco elixir** (Hyoscyamine)
- **Hyospaz** (Hyoscyamine)
- **Hyosyne** (Hyoscyamine)
- **Hysosol** (Hyoscyamine)
- **Janamine** (Imipramine)
- **Levbid** (Hyoscyamine)
- **Levsin** (Hyoscyamine)
- **Levsin/SL** (Hyoscyamine)
- **Levsinex Timecaps** (Hyoscyamine)
- **Losamine, M** (Hyoscyamine)
- **Norpramin**, (Desipramine)
- **Oxytrol patch** (Oxybutynin)
- **Pamelor** (Nortriptyline)
- **Pertofrane** (Desipramine)
- **Pro-Banthine** (Propantheline)
- **Pro-Banthine** (Propantheline Bromide)
- **Quarzan** (Clidinium)
- **Robinul** (Glycopyrrolate Tablets)
- **Robinul Forte** (Glycopyrrolate Tablets)
- **Sinequan** (Doxepin)
- **Surmontil** (Trimipramine)
- **Tofranil** (Imipramine)
- **Tofranil PM** (Imipramine Pamoate)
- **Vivactil** (Protriptyline)

ATTACHMENT B

DRY MOUTH HANDOUT

BE-DRI

DRY MOUTH

If you develop dry mouth, the following should be helpful with symptoms:

1. Chew sugar-free gum.
2. Suck on sugar-free hard candy.
3. Sip on water, especially during meals to help swallow food.
4. Use fluoride toothpaste to help prevent dental cavities.
5. Avoid mouthwashes with alcohol.
   Try 1 tsp salt and 1 tsp baking soda in a quart of water as a mouthwash.
6. Use an oral lubricant, available over-the-counter located near the toothpastes.

ATTACHMENT C

CONSTIPATION HANDOUT

CONSTIPATION

BE-DRI

Constipation is defined as the passage of hard stools less than three times a week or difficulty passing stools. Contrary to popular belief, it is not necessary to have a bowel movement every day. "Normal" bowel movements vary from person to person. Many things, such as not drinking enough fluids, lack of physical activity, a diet low in fiber, and even certain medicines may contribute to the problem. Sometimes, but not often, constipation may be due to serious medical problems. If you become constipated, it is wise to speak to your physician about the problem so that serious illness can be ruled out.

Regular use of a laxative, especially for a long time, can actually cause constipation rather than relieve it. When you use laxatives regularly, you interrupt the body's normal way of emptying waste. Overuse of mineral oil may reduce the absorption of certain vitamins (A, D, E, and K). Some laxatives can interfere with the medications your doctor has prescribed for you. When you stop using laxatives after a long period of time, you may find that you cannot have a bowel movement without them. However, it is still possible to break this cycle.

Although many laxatives may be used on occasion, never use them for more than a week, unless your doctor prescribes them. Instead, try to prevent or relieve constipation by using more natural measures:

1. **Drink enough fluids** such as water, or other caffeine free, non-alcoholic fluids: the equivalent of six to eight glasses a day -(unless your doctor instructs you otherwise).

2. **Increase fiber in your diet**. The average American diet contains 10-15 grams of fiber a day. The recommended intake of fiber is 20-25 grams per day. Good sources include bran and whole-grain cereals and breads, fruit, fresh vegetables, and beans. In order to avoid feeling "bloated" or "gassy," slowly increase dietary fiber over several weeks. Prune juice, apples, and pears seem to work particularly well for some people.

3. **Exercise regularly**. A daily walk for at least 15 minutes (more if you can) will help not only your bowels, but also your heart, muscles, and over-all attitude toward life. If you are not exercising regularly, be sure to check with your doctor before beginning a new program.

4. **Try to develop a regular bowel habit**, such as attempting to have a bowel movement after breakfast or dinner each day. Some people prefer to have their bowel movements only at home, but delaying a bowel movement can actually lead to constipation. Response to the natural urge as quickly as possible even if you are away from home.

5. **Take an over-the-counter psyllium-based fiber supplement**. These are not laxatives, but they increase the amount of the water content in your stool, making it softer and easier to pass. These can be taken in pill or capsule form or as granules mixed in water or juice. They are taken on a daily basis to prevent constipation. Be sure to include additional water in your diet if you take extra fiber: these liquids will become part of your elimination in your stool instead of your urine.

6. **Avoid powerful laxatives** containing cascara, senna, or sennoside, unless prescribed by your doctor. When you do need a laxative, ask your doctor what he or she recommends. Docusate (a stool softener), Milk of Magnesia, glycerin suppositories, or mineral oil are common choices. Be sure you do not use them for longer than a week. If you are currently "hooked" on laxatives, you may need to wean yourself off over a period of several weeks. At the same time you should be careful to drink plenty of water, exercise regularly (both with your doctor's permission), and increase the fiber in your diet and/or include a fiber supplement (See 2 and 5 above).

7. **Please consult your doctor** if you have blood in your stool, unexplained weight loss, severe constipation, or a change in bowel habits. The constipation may be a sign of other health problems.

Provided courtesy of University of Alabama at Birmingham

ATTACHMENT D

FLUID MANAGEMENT HANDOUT

FLUID MANAGEMENT INSTRUCTIONS

- The average fluid intake for a healthy adult is considered to be 50 to 70 ounces of liquid each day. This means that each day you should consume the equivalent of 6 to 8 eight-ounce glasses of liquids (including any beverages and soups), much of which can be in the form of solid foods.

- This should produce a healthy 40-50 ounces of urine in 24 hours. If you voided much more than this volume on your diary, you may want to adjust your intake to produce more normal amounts of urine. People who work in hot climates or exercise heavily need more fluids because of loss through perspiration, but their urine output should still be approximately 40-50 ounces.

- Spread out your consumption of liquids rather than consuming a lot at one time, and try to avoid fluids within a few hours of going to bed. Don't drink fluids overnight.

- If your urine output is less than 40 ounces in 24 hours, and cannot be explained by losses due to urine leakage, you may need to drink more fluids.

ATTACHMENT E

APPOINTMENT LOG

BE-DRI

APPOINTMENT LOG

Name: _____

Visit 1: _____ _____
Date Time

Visit 2: _____ _____
Date Time

Visit 3: _____ _____
Date Time

Visit 4: _____ _____
Date Time

Visit 5: _____ _____
Date Time

If you have any questions, please call the study nurse:

Name: _____ **Phone Number:** _____

Please remember to bring your pill bottle and this Appointment Log to every visit.

ATTACHMENT F

INSTRUCTIONS FOR DAILY PELVIC FLOOR MUSCLE EXERCISE

BE-DRI

INSTRUCTIONS FOR DAILY PELVIC FLOOR MUSCLE EXERCISE

- **Continue to keep your bladder diary.**
- **Do 45 pelvic floor muscle exercises <u>EVERY</u> day:**

  15 at a time, 3 times per day.

  - **Do ____ lying down**
  - **Do ____ sitting**
  - **Do ____ sitting (or standing)**

  - **For each exercise, squeeze your pelvic floor muscles as quickly and as hard as you can.**

  Hold the squeeze for:

  - **1 Second**
  - **3 Seconds**
  - **6 Seconds**
  - **8 Seconds**
  - **10 Seconds**

  Relax completely between each squeeze for:

  - **2 Seconds**
  - **6 Seconds**
  - **12 Seconds**
  - **16 Seconds**
  - **20 Seconds**

- **Remember to relax all the muscles in your abdomen when you do these exercises and continue to breathe normally.**

Other instructions: _____

_____

When you begin this exercise program, you may notice that the muscles seem weak or hard to stay contracted very long. This will improve as the muscle becomes stronger and builds better endurance.

You should not expect to experience pain as a result of pelvic floor muscle exercise. If you experience pain in your back, hips, or the area around you vagina or anus, you might be exercising incorrectly. If this situation occurs, call your interventionist

_____, at (___ ___)_____

Helpful Hints for Pelvic Floor Muscle Exercises

In women, important pelvic organs (the bladder, uterus, and bowel) are supported by muscles and other tissues. Stress incontinence occurs when the supportive structures weaken. Stress incontinence typically occurs with a sneeze, cough, lifting a heavy object, or during exercise. Urge incontinence, on the other hand, occurs when the bladder muscle contracts at the wrong time, causing urine to be pushed out.

Exercising the pelvic floor muscles can help reduce both forms of incontinence. This handout will help you understand the muscles and how to exercise them better.

The pelvic floor muscles, called the levator ani muscles, attach to your pelvis in a way that creates a "sling or hammock-like" support. These muscles support the pelvic organs and help prevent urine leakage.

The following tips may help you exercise these muscles effectively.

1. Recognizing the right muscles to contract is important. The muscles you need to work are the same muscles you would use to hold back gas or a bowel movement. When you squeeze these muscles, you should feel a tightening around your vagina and anus. As these muscles get stronger, think about drawing the pelvic floor (the area around your vagina and anus) "up and inward".

2. Breathe during the exercises. Holding your breath can raise your blood pressure. If you have difficulty breathing, count aloud while you contract your muscles. This will force you to breathe while you exercise.

3. Do not "bear down" or push when you exercise. This will cause strain on your pelvic floor. Instead, you need to think about drawing the pelvic floor upwards, like an elevator.

4. Tensing your stomach muscles can also place a strain on your pelvic floor. Place a hand on your abdomen as you exercise. This will help you tell if you are tensing these muscles instead of the pelvic floor muscles.

5. Relax your muscles completely between each contraction for the entire time recommended by your interventionist. Relaxing the muscle between each contraction allows blood and oxygen to flow to the muscle. Proper relaxation will prevent your muscles from getting too tired.

ATTACHMENT G

PATIENT RECOMMENDATIONS BASED ON EXERCISE BARRIERS

BE-DRI

PATIENT RECOMMENDATIONS BASED ON EXERCISE BARRIERS

1. *It was hard to find the time to do all of the exercises*.

   Recommendations:

   Do not be judgmental. Instead, discuss with the patient if there are periods most suitable for exercise for example, exercises could be done while watching TV or right before going to bed. Also explore if patient would be able to more consistently perform a smaller number of exercises. Ask her the number that would work and then readjust from there.

   Explore if the problem is that she just does not like to exercise. Again, show understanding for her dislike of exercise. But reinforce that the exercises are just as important as medication in treating this problem and that they have the potential for making a large difference in her function. Also, review the diary for any improvements and use rewarding language to help motivate continued performance.

2. *I was not sure if I was doing them correctly*.

   Recommendations: Reassure the patient that this will be reviewed with her each visit using digital palpation.

3. *The exercises caused pain*.

   Recommendations: Pain might be a cue that she is using more accessory muscles. Check for this during the reexamination, particularly if she is arching her back. If she has back pain, suggest placing pillows under legs during exercise as an alternative position for supine. Explore type of pain, muscle soreness versus sharp type pain or radiating pain. If pain is muscle soreness, it is likely due to muscle fatigue. May suggest lowering repetitions until patient improves tolerance. If sharp or radiating, stop exercises and consult MD.

4. *I often forgot to do the exercises*.

   Recommendations: Have patient place reminders in her environment. Try a sign on the bathroom mirror, "did you exercise today", etc.

5. *The exercises did not seem to be helping my incontinence*.

   Recommendations:

   Early on, explain that exercises take time to help. Assure patient that she has not been doing them that long and continue to monitor this. Could be that patient is also doing them incorrectly. She may also have unrealistic expectations. Review diary to determine if she is in fact doing better; if so, reinforce this with the patient.

   Also reinforce that she should not be getting worse, but perhaps she did more activity in the last week or changed her diet somehow to cause more bladder irritation. Explore these issues with her. Also, make sure she is not straining during the exercise. If this continues contact the MD.

6. *I am so much better and did not feel that I need to continue with the exercises*.

   Recommendations: Tell her that it is great she is better, but that it is important to continue the exercises to make sure her improvements are stable.

7. *Taking the medication for incontinence is more important than doing the exercises*.

   Recommendations: Like #1, reinforce the value of exercise by itself.

ATTACHMENT H

BEHAVIORAL STRATEGY PROBLEM CHECKLIST

BE-DRI

BEHAVIORAL STRATEGY PROBLEM CHECKLIST

Early on, you might find that using behavioral strategies is difficult, particularly in certain situations. I am going to ask you some questions to help identify the problems you are having controlling you leakage.

1. Did you use the urge suppression strategy?
   □ yes □ no

2. Did the urge suppression strategy work for you?
   □ yes □ no

3. If yes, how often did the urge suppression strategy work?
   □ all the time □ some of the time □ never

4. Did the urge suppression strategy control the urge at first, but then the urge came back before you could get to the toilet?
   □ yes □ no

5. Did you find that the leakage started so suddenly that there wasn't time to use the urge suppression strategy?
   □ yes □ no

If you taught urge <u>avoidance</u> strategies at Visit 3 because urge suppression strategies were ineffective, ask question 6 and 7 at Visit 4.

6. Did you use the urge avoidance strategy?
   □ yes □ no

7. Did the urge avoidance strategy work for you?
   □ yes □ no

If patient voids >8 times per day ask question 8.

8. Have you been able to delay voiding at least 10 minutes by using the urge strategy?
   □ yes □ no

If the patient also has stress accidents on the bladder diary continue with questions 9-11.

9. Did you use the stress strategy?
   □ yes □ no

10. How often did the stress strategy work for you?
    □ all the time □ some of the time □ never

11. Did you find that the leakage started so suddenly that there wasn't time to use the stress strategy?
    □ yes □ no

ATTACHMENT I

PATIENT RECOMMENDATIONS BASED ON BEHAVIORAL STRATEGY PROBLEM CHECK LIST

BE-DRI

PATIENT RECOMMENDATIONS BASED ON BEHAVIORAL STRATEGY PROBLEM CHECK LIST

1. *Not using the urge strategy*.

   Recommendations: Emphasize that the pelvic floor muscle exercises she has been doing are important to strengthen them, and that using the muscles when she needs them is the next step to gaining control of her bladder.

2. *The strategy did not work.*

   Recommendations: Explain that this will get better with practice as she gets more skilled and her muscles get stronger. Ask her to describe what she is doing as she uses the urge strategy. Helpful hints include (a) paying attention to urges earlier when they are easier to suppress (b) stand/sit still while doing the urge strategy, not while walking to the bathroom, (c) not to relax the muscles between contractions (as when doing exercises) when she is doing the urge strategy (squeeze the pelvic floor muscles hard initially and then tighten them with each successive squeeze, kind of like she is ratcheting the muscle closed, (d) once the urge is suppressed, go to the bathroom despite the disappearance of the urge. Inquire about the incidences when the strategy failed (use the bladder diary) and use these to make specific suggestions.

   Tell her to avoid provocative situations when her bladder is full. Many people report that their urge is worst when arriving home, putting the key in the door, running water, etc. It is easier to make the urge go away when her bladder is empty, so try to empty her bladder before driving home or performing activities that involve running water. She may still experience an urge, but she will be more successful in suppressing the urge in these situations if her bladder is less full.

3. *The strategy controlled the urge at first, but then the urge came back before she could get to the toilet*.

   Recommendations: Repeat the urge strategy immediately. Try the "freeze and squeeze." DON'T RUN! Instead, stop ("freeze") and squeeze her pelvic floor muscles. Think about a mental image of the bladder contraction that is producing the urge, and make that bladder contraction go away. Thus, if the urge returns on the way to the bathroom or in the bathroom before reaching the toilet, stop and stand still, squeeze the pelvic floor muscles several times until the urge is under control, then proceed to the toilet.

4. *The leakage started so suddenly that there wasn't time to use the strategy*.

   Recommendations: Try to identify activities that ordinarily trigger leakage (such as standing up from a chair, getting out of bed, putting your key in the front door, or running water) and don't wait for the sudden urge or leakage to occur. Anticipate them by using the urge strategy even before the urge or the leakage occurs. Use the bladder diary as a guide for urge triggers. For example, always squeeze your pelvic floor muscles as you stand up if this is one of your triggers. If you have "key in the door" syndrome, squeeze *before* you put the key in the door or even earlier.

5. *Was unable to delay going to the toilet for 10 minutes.*

   Recommendations:

   - Encourage any progress thus far and back up to a more achievable delay time. Compare most recent bladder diaries to baseline diaries and note progress with decreasing voiding frequency and increasing voiding intervals.

   - Try delaying voiding just 2 or 3 minutes rather than 10, until she gains confidence. Then progress the delay interval.

   - Use the urge suppression strategy repeatedly each time the urge returns to achieve the desired delay. Try distraction techniques while waiting for the suggested delay time.

   - Suggest she try delaying voiding during safe times, such as at home.

6. *Did not use the stress strategy*.

   Recommendations: Emphasize that the pelvic floor muscle exercises she has been doing are important to strengthen them, and that using the muscles when she needs them is the next step to gaining control of her bladder.

7. *The stress strategy did not work.*

   Recommendations: Explain that this will get better with practice as she gets more skilled and her muscles get stronger. Tell her to use the bladder diary to identify the situations that cause leakage, so that she can squeeze her pelvic floor muscles in anticipation of possible leakage (coughing, sneezing, blowing nose, picking up something heavy).

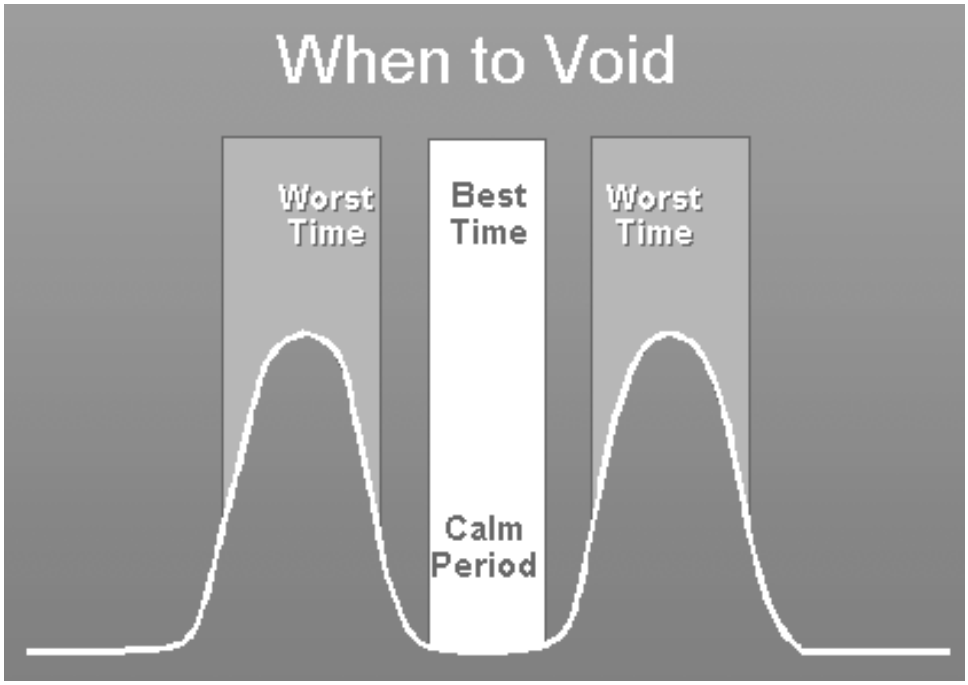
8. *The precipitant (cough, sneeze, etc.) occurred so suddenly that there wasn't time to use the stress strategy*?

   Recommendation - Show understanding that they do happen very fast. Ask her if she was able to cover her mouth with her hand as she sneezed. Remind her that this was a learned skill and with practice she can squeeze her pelvic floor muscles just that fast. It will actually become automatic with time.

ATTACHMENT J

Handout of Urge Suppression Strategy

Handout of Urge Suppression Strategy



When the Urge Strikes..

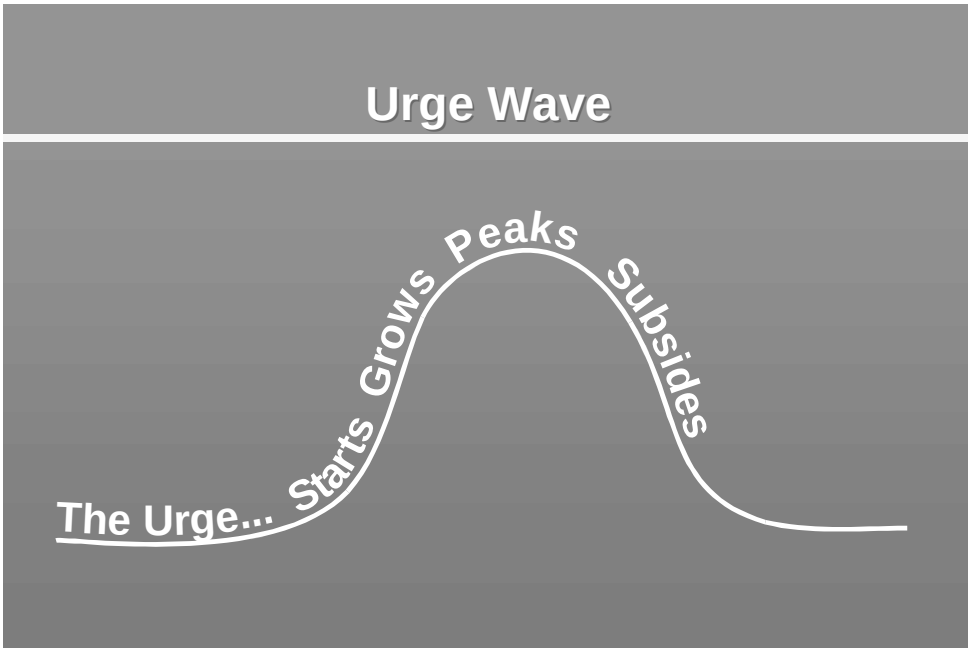
- Stop and stay still. Sit down if you can.
- Squeeze your pelvic floor muscles quickly 3 to 5 times and repeat as needed.
- Relax the rest of your body. Take a deep breath.
- Concentrate on suppressing the urge.
- Wait until the urge subsides.
- Walk to the bathroom at a normal pace.

ATTACHMENT K

Handout of Urge Suppression Strategy for Patients in Bladder Training

BE-DRI

Handout of Urge Suppression Strategy for Patients in Bladder Training



When the Urge Strikes..

- Stop and stay still. Sit down if you can.
- Squeeze your pelvic floor muscles quickly 3 to 5 times and repeat as needed.
- Relax the rest of your body. Take a deep breath.
- Concentrate on suppressing the urge.
- Distract yourself. Get your mind on something else.
- Delay going to the bathroom for ____ minutes.
- Walk to the bathroom at a normal pace.

ATTACHMENT L

Stress Strategies

Stress Strategies

Stress leakage results when the pressure of pushing urine out is higher than the pressure of holding the urine in, such as during a sneeze.

Now that you have learned to exercise your pelvic floor muscles, it is time to USE them to prevent stress incontinence.

Think of any activities that have caused you to leak urine:

Coughing?
Sneezing?
Lifting?
Getting up from a chair?

Others: _____

_____

_____

_____

To prevent urine loss, tighten your pelvic floor muscles as fast and hard as you can just ***before*** and ***during*** these activities.

The Stress Strategy requires careful timing and practice. Don't get discouraged. Eventually, it will become automatic.

If you forget to tighten your muscles and urine leaks out, go ahead and squeeze your muscles right then. It won't prevent *that* accident, but it will help you develop the habit of tightening the muscles with that activity in the future.

Remember: "Squeeze before you sneeze."

APPENDIX C: DRUG-ONLY TREATMENT PROTOCOL

BE-DRI

Drug-Only Treatment Protocol

Overview

The drug-only treatment program will be conducted in 4 visits separated by two to three week intervals over a period of not more than 10 weeks. While the drug-only arm of the trial is meant to simulate 'standard-care', treatment activities included in the drug-only intervention will be specified to establish a Network-wide standard that will provide BE-DRI staff with clear guidelines for all drug-only intervention activities. This standardization will ensure that the drug-only intervention is provided in the same manner to all patients both within and across clinical centers. It will also minimize contamination of drug-only patients with unintended behavioral treatment advice.

The objective for each drug treatment visit is threefold:

- Deliver the basic elements of **standard care drug treatment** including drug distribution; evaluation of adherence with the prescribed drug regimen; and assessment and treatment of side effects (symptoms) that may be related to use of the study drug. The drug intervention component of each intervention visit is the same in both treatment arms.
- Provide some degree of **social contact** for drug-only patients to parallel that in the behavioral treatment arm. The drug-only treatment program, as designed, will provide the necessary social contact for the drug-only patients to mimic the social contact effects that will naturally accompany the BE-DRI behavioral program.
- Maximize accuracy in completion of **bladder diary** documentation.

Drug-only patients will also be instructed to complete bladder diaries throughout the intervention period. Since a 7-day bladder diary is used as the primary outcome measure, accuracy in record keeping is essential to achieve the aims of the BE-DRI Trial. The Interventionist will conduct reviews of the completed diaries to check diaries for legibility and completeness. While maintenance of a bladder diary is generally considered a critical element of a behavioral intervention program, diaries are incorporated in the drug-only arm of the trial to hone skills in bladder dairy maintenance and documentation for drug-only patients to maximize accuracy in record keeping for this important primary outcome measure.

Standard Drug Therapy

The drug therapy selected for use in the BE-DRI trial is a 4mg daily dose of tolterodine tartrate extended release capsule, trade name Detrol LA. During the 10-week intervention period, one break from drug treatment of ≤7 days is allowable, recognizing that such a break might be clinically indicated; e.g. during treatment of another illness. Some patients may report bothersome side effects during or between study visits. Uniform interventions have been developed for the common side effects of dry mouth and constipation. All other bothersome side effects will be treated at the discretion of the Interventionist in accordance with her customary clinical practice. The daily dose of Detrol LA may be decreased to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level. Detrol LA may be discontinued at the discretion of the Interventionist if the patient continues to suffer from intolerable side effects, although the need to discontinue drug therapy altogether should be uncommon. In a Phase 3 controlled clinical trial, Pfizer found treatment with Detrol LA 4mg daily was discontinued due to adverse events in 2.4% of patients taking Detrol LA. (http://www.pfizer.com/download/uspi_detrol_la.pdf).

Subsequent study visits should still be conducted per protocol for patients who stop taking Detrol LA.

Drug-Only Treatment Visit 1

At the time patients are randomized and introduced to the Interventionist, they will have completed the 7-day baseline bladder diary and the self-administered Symptoms Checklist, data form 205 (FM205).

Bladder Diary Review

Completing the Review

The dairy review completed for drug-only patients will be limited to a minimal review; Interventionists review the diary for completeness **only,** to be certain all essential elements are included and all of the patient's recordings are legible and codable. Interventionists should also remind the patient of the proper methods of completing the bladder diary accurately as needed. Refer to the Bladder Diary Procedures for a description of elements required for a complete Diary.

Diaries are reviewed to assure that patients in the drug-only arm become equally skilled in maintaining an accurate record of voiding and incontinent events as compared to patients in the combination treatment group. Therefore, the objectives of the diary review for the drug-only patient is to maximize the patient's skills/abilities in maintaining a legible and complete record including the timing, frequency and circumstances of all incontinent episodes over the course of the 7-day period. A secondary benefit of multiple dairy reviews will be fewer invalid diaries in the post-intervention visits. Hence, fewer patients will be required to repeat this burdensome 7-day diary required for determination of the outcome of the treatment protocol under study.

Avoiding Contamination

Interventionists must strictly avoid any and all behavioral tips that may be associated with the diary review that they might otherwise offer urinary incontinence patients.

The following recommendations are strictly forbidden:

- Altering fluid intake
- Altering voiding patterns
- Kegel exercises
- Any use of pelvic floor muscles
- Dietary alterations

Several data points must be recorded on the Intervention data form i.e. average number of leaks per week and average number of voids per 24-hour period. While these data are required for the data form they should never be shared or discussed with patient in the drug-only arm. The calculations should not be made in the presence of the patient.

Standard Drug Therapy

Prescribing and Dispensing Detrol LA

Detrol LA 4 mg daily, is prescribed during the baseline study visit (Visit 0), and patients are given a 30-day supply of Detrol LA at the first intervention visit (Visit 1). Each clinical center will make arrangements for the dispensing of Detrol LA in accordance with their center's institutional policies pertaining to the dispensing of prescribed medication. NOTE: *Detrol LA is not an experimental drug.*

Standard Drug Education/Information

A Detrol LA Information Handout has been developed specifically for the BE-DRI trial and is given to all patients at Visit 1 (Attachment A). The Interventionist delivers the standard study drug education by thoroughly reviewing the handout with the patient.

Patients should be instructed to bring their bottle of Detrol LA with them when they return to the center for each of their study visits as an actual pill count must be completed at all subsequent intervention visits to evaluate adherence with drug therapy.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist next reviews all "yes" symptoms on the Symptoms Checklist and initiates treatments or makes recommendations for bothersome symptoms if indicated. If the patient complains of problems with dry mouth or constipation, standardized advice for these complaints will be offered and the information handouts developed for these 2 common complaints are given to the patient (Attachments B and C). Other recommendations/interventions may be offered for all other bothersome symptoms in accordance with the individual Interventionist's standard practice.

Fluid Management

Giving the Fluid Management Handout

All patients receive the BE-DRI Fluid Management Handout containing general recommendations about fluid intake and output (Attachment D).

Avoiding Contamination

To prevent inadvertent contamination of patients in the drug-only treatment arm, it is essential that Interventionists refrain from providing non-authorized advice about fluid management, or any other behavioral treatment advice. This includes recommendations or counseling during this or ANY other study visit.

Appointments

An appointment for a return visit in 2 weeks and appointments for *all remaining* intervention visits should be made at this time. An Appointment Log is available for this purpose (See Attachment E).

Ideally, the 4 intervention visits are scheduled evenly throughout the 10-week intervention period. The following table provides a guide for scheduling the visits.

Visit Target Days:	Visit 2: Treatment Day 14
	Visit 3: Treatment Day 28
	Visit 4: Treatment Day 49
	Visit 5: Treatment Day 70

Use this table as a guide when scheduling the visits. Some leeway is allowed for extenuating circumstances, but every effort should be made to keep the patient on a strict schedule for the intervention visits. Details about the limits of compressing or stretching the required study visit windows are described elsewhere.

Note: the shorter, 2-week time interval between the earlier visits is intended to allow better management in the earlier weeks; the window following Visits 3 and 4 increases to 3 weeks. Following this guideline will permit visit scheduling on the same weekday throughout the intervention period, which will likely be a convenience for most patients.

Patient Materials

Patients are sent home with:

- 30-day supply of Detrol LA 4mg
- Detrol LA Information Handout (Attachment A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Fluid Management Handout (Attachment D)
- Appointment Log (Attachment E)
- Diaries, enough to complete continuously between visits. The interventionist encourages accuracy and consistency in completing the diaries.

Documentation

All critical activities and measurements completed at Visit 1 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 1. (FM211).

Drug Only Treatment Visit 2

Symptoms Checklist

The patient should complete the Symptoms Checklist (FM205) in the waiting area prior to the start of the visit with the Interventionist.

Bladder Diary Review

The Interventionist reviews the bladder diaries for completeness and legibility making certain that all essential elements are included and all patient recordings are legible and codable. The Interventionist should also reinforce good record keeping and review proper record keeping for the areas that require improvement.

Avoiding Contamination

As previously described, it is critical that the Interventionist avoids any and all behavioral tips that may be associated with diary review that she might otherwise offer to urinary incontinence patients.

The following recommendations are strictly forbidden:

- Altering fluid intake
- Altering voiding patterns
- Kegel exercises
- Any use of pelvic floor muscles
- Dietary alterations

Several data points must be recorded on the Intervention data form i.e. average number of leaks per week and average number of voids per 24-hour period. While these data are required for the data form they should never be shared or discussed with patient in the drug-only arm. The calculations should not be made in the presence of the patient.

Medication Audit Update

The Interventionist asks the patient if she has started taking any of the medications listed on the Detrol LA Information Handout, i.e. "Need-To-Know" medications.

Standard Drug Therapy

Adherence to the Drug Regimen

Next, the Interventionist completes the pill count and interviews the patient to evaluate the level of adherence with the prescribed drug regimen.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist also reviews all "yes" symptoms on the Symptoms Checklist with the patient. Bothersome side effects reported by the patient on the Checklist (FM205) or in conversations with the Interventionist during or between study visits are treated at the discretion of the Interventionist in accordance with her customary clinical practice. Uniform interventions developed for the common side effects of dry mouth and constipation should be used for these complaints (Attachments B and C).

Decreasing the dose or discontinuation of Detrol LA

The daily dose of Detrol LA may be decreased to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level to the patient. Detrol LA may be discontinued at the discretion of the Interventionist if the patient continues to suffer from intolerable side effects but every effort should be made to help the patient continue on the medications.

Subsequent study visits should still be conducted on schedule for patients who stop taking Detrol LA.

Dispensing Detrol LA

The initial 30-day supply of Detrol LA dispensed at Visit 1 should be sufficient to last until Visit 3. If for any reason the Interventionist believes this supply will be inadequate to cover the days until the next study visit, patients should be provided with another 30-day supply of Detrol LA at Visit 2.

If the Detrol LA dose is decreased to 2mg, a 30-day supply of the Detrol LA 2mg capsules will be dispensed. Any remaining 4 mg capsules must be returned to the Interventionist. Likewise, if Detrol LA is discontinued altogether, all remaining capsules should be returned to the Interventionist.

Appointments

At the close of the visit, the Interventionist should review and confirm dates and times for all subsequent intervention visits. The Appointment Log should be used for this review and corrected if appointment times and/or dates are changed.

The Interventionist should also contact the Study Nurse/Interviewer to confirm the patient's appointment day and time for Visits 5.

Patient Materials

Patients are sent home with:

- Sufficient supply of Detrol LA
- Detrol LA Information Handout as needed (Attachments A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Appointment Log (Attachment E)
- Bladder Diaries: The Interventionist encourages accuracy and consistency in completing the diaries.

Documentation

All critical activities and measurements completed at Visit 2 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 2. (FM222).

If the Interventionist has contact with the patient between Visit 1 and Visit 2, a record of the contact including any measurements or interventions completed should be recorded in real time in a medical record or other source document. Selected data will also be abstracted onto the Data Form for Visit 2. (FM222).

Drug Only Treatment Visit 3

Symptoms Checklist

The patient should complete the Symptoms Checklist (FM205) in the waiting area prior to the start of the visit with the Interventionist.

Bladder Diary Review

The Interventionist reviews the bladder diaries for completeness and legibility making certain that all essential elements are included and all patient recordings are legible and codable. The Interventionist should also reinforce good record keeping and review proper record keeping for the areas that require improvement.

Avoiding Contamination

As always, it is critical that Interventionists avoid any and all behavioral tips that may be associated with diary review that might otherwise be offered to urinary incontinence patients. Although several data points must be recorded on the intervention data form i.e. average number of leaks per week and average number of voids per 24-hour period, they should not be shared or discussed with the patient.

Medication Audit Update

The Interventionist again asks the patient if she has started taking any of the medications listed on the Detrol LA Information Handout, i.e. "Need-To-Know" medications.

Standard Drug Therapy

Adherence to the Drug Regimen

The Interventionist next completes the pill count and interviews the patient to evaluate the level of adherence with the prescribed drug regimen.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist again reviews any "yes" symptoms on the Checklist and treats bothersome side effects as needed using the uniform interventions for complaints of dry mouth and constipation (Attachments B and C). All other bothersome symptoms are treated at the discretion of the Interventionist in accordance with her customary clinical practice.

Decreasing the dose or discontinuation of Detrol LA

As previously described, Detrol LA may be decreased from 4mg to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level. And Detrol LA may be discontinued if the patient continues to suffer from intolerable side effects.

Subsequent study visit should still be conducted on schedule for patients who stop taking Detrol LA.

Dispensing Detrol LA

Another 30-day supply of Detrol LA will be dispensed at Visit 3 if a second bottle of 30 capsules was not dispensed at Visit 2. If for any reason the Interventionist believes this supply will be inadequate to cover the days until the next study visit, patients will be provided with a sufficient supply of Detrol LA to last through Day 70, i.e. end of Stage 1

If the Detrol LA dose is decreased to 2mg, a 30-day supply of the Detrol LA 2mg capsules will be dispensed.

Any remaining 4 mg capsules must be returned to the Interventionist. Likewise, if Detrol LA is discontinued altogether, all remaining capsules should be returned to the Interventionist.

Appointments

The Interventionist should review and confirm the date and time for the Visit 4. The Appointment Log should be used for this review and corrected if appointment times or dates are changed.

Patient Materials

Patients are sent home with:

- Sufficient supply of Detrol LA
- Detrol LA Information Handout as needed
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Appointment Log (Attachment E)
- Bladder Diaries: The Interventionist encourages accuracy and consistency in completing the diaries.

Documentation

All critical activities and measurements completed at Visit 3 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 3. (FM233).

If the Interventionist has contact with the patient between Visit 2 and Visit 3, a record of the contact including any measurements or interventions completed should be recorded in real time in a medical record or other source document. Selected data will also be abstracted onto the Data Form for Visit 3. (FM233).

Drug Only Treatment Visit 4

Symptoms Checklist

The patient should complete the Symptoms Checklist (FM205) in the waiting area prior to the start of the visit with the Interventionist.

Bladder Diary Review

Once again, the Interventionist reviews the bladder diaries for completeness and legibility making certain that all essential elements are included and all patient recordings are legible and codable. The Interventionist should also reinforce good record keeping and review proper record keeping for the areas that require improvement.

Avoiding Contamination

As always, it is critical that Interventionists avoid any and all behavioral tips that may be associated with diary review that might otherwise be offered to urinary incontinence patients. Although several data points must be recorded on the intervention data form i.e. average number of leaks per week and average number of voids per 24-hour period, they should not be shared or discussed with the patient.

Medication Audit Update

The Interventionist again asks the patient if she has started taking any of the medications listed on the Detrol LA Information Handout, i.e. "need-to-know" medications.

Standard Drug Therapy

Adherence to the Drug Regimen

The Interventionist next completes the pill count and interviews the patient to evaluate the level of adherence with the prescribed drug regimen.

Review of the Symptoms Checklist and Interventions for Bothersome Symptoms

The Interventionist again reviews any "yes" symptoms on the Checklist and treats bothersome side effects as needed using the uniform interventions for complaints of dry mouth and constipation (Attachments B and C). All other bothersome symptoms are treated at the discretion of the Interventionist in accordance with her customary clinical practice.

Decreasing the dose or discontinuation of Detrol LA

As described in Visit 2, Detrol LA may be decreased from 4mg to 2 mg if all reasonable palliative interventions fail to reduce side effects to a tolerable level. And Detrol LA may be discontinued if the patient continues to suffer from intolerable side effects.

Subsequent study visits should still be conducted on schedule for patients who stop taking Detrol LA.

Dispensing Detrol LA

At this last intervention visit, the Interventionist should dispense only the exact amount of Detrol LA that will be required to permit the patient to continue drug therapy to the end of the intervention period, i.e. Day 70. Count the **exact** number of days remaining between the actual study Visit 4 and Day 70 and only dispense this **exact** number of capsules. Recover as many capsules as necessary to be sure the patient only has this exact amount. Patients should not continue drug therapy beyond day 70 even if they took drug less than 70 days because of a break in therapy earlier in the intervention.

If the Detrol LA dose is decreased to 2mg, dispense the exact number of 2mg capsules that will be required to continue drug therapy to the end of the intervention and recover any remaining 4 mg capsules. Likewise, if Detrol LA is discontinued altogether, all remaining capsules must be returned to the Interventionist.

Preliminary Discussion of Stage 2 Activities

Because this is the last contact between the Interventionist and patient, the Interventionist also explains the importance and function of completing the drug-therapy through the end of Stage 1, i.e. Day 70. If for any reason the patient misses any doses, she should not take Detrol LA beyond Day 70. All remaining capsules should be returned to the Study Nurse at Visit 5. If the patient takes all the capsules, she should return the empty bottle at Visit 5.

The Interventionist also reminds the patient that Visit 5 marks the end of Stage 1 and the beginning of Stage 2. Details about the Stage 2 activities are reviewed briefly at this time. They will be provided to the patient in a written form at the end of Stage 1. The written details, described in the body of a Thank-you letter, can be hand delivered to the patient at Visit 5 or they can be mailed to the patient for a receipt date that will coincide with the last day of Stage 1.

Appointments

At the end of Visit 4 the Interventionist confirms the day, date and time of the patient's Visit 5 with the BE-DRI Study Nurse / Interviewer. Ideally, the Interventionist will call the Interviewer to confirm the appointment time and verify or correct the patient's Appointment Log as needed.

Patient Materials

Patients are sent home with:

- Exact number of Detrol LA capsules required for the completion of Stage 1
- Detrol LA Information Handout as needed (Attachment A)
- Dry Mouth Handout as needed (Attachments B)
- Constipation Handout as needed (Attachment C)
- Evaluation Bladder Diaries*
- Appointment Log (Attachment E) with the confirmed appointment day and time for Visit 5

* Only one 7-day diary is needed at Study Visit 5, so Interventionists should instruct patients to complete only one 7-day diary during the last week of the intervention. This diary must be completed while the patient is still on drug therapy. In preparation for Visit 5, the Interventionist reinforces the importance of keeping accurate diaries. Patients are reminded that this 7-day diary is essential for measuring any changes in their continence status before and after the intervention. In addition to tracking voiding and

accident events the patient must again measure intake and output for 2 of the 7 days and complete the urgency rating scale for every accident and void on 2 of 7 days.

Documentation

All critical activities and measurements completed at Visit 4 must be recorded in a source document and on the BE-DRI Intervention Data Form for Visit 4. (FM233).

If the Interventionist has contact with the patient between Visit 3 and Visit 4, a record of the contact including any measurements or interventions completed should b recorded in real time in a medical record or other source document. Selected data will also be abstracted onto the Data Form for Visit 4. (FM233).

Drug-Only Treatment Patient
Post-Treatment Visit 5: End of Stage 1

Recovery of unused Detrol LA capsules

Because this is the end of Stage 1, the Study Nurse must recover all doses of unused Detrol LA. All remaining capsules must be recovered. If the patient took all the capsules, she should return the empty medication bottle at Visit 5.

Delivery of Written Reminder of Stage 2 Activities

At Visit 5, patients are given the "Thank-you" Letter (prepared at the end of Visit 4 by the Interventionist) that officially recognizes the end of Stage 1 and reminds the patient of Stage 2 study activities.

The "Thank-You" Letter can be sealed in an envelope addressed to the patient and delivered to her via the BE-DRI Study Nurse /Interviewer at Visit 5 or it can be mailed directly to her home with a receipt date that will coincide with the end of Stage 1.

Documentation

The Interventionist will be required to complete a data form at the end of the Intervention to document all required intervention activities have been completed. If the Interventionist has contact with the patient between Visit 4 and Visit 5, a record of the contact including any measurements or interventions completed should be recorded in real time in a medical record or other source document. Selected data will also be abstracted onto a BE-DRI Data Form.

ATTACHMENTS FOR THE DRUG-ONLY TREATMENT

ATTACHMENT A

INFORMATION ABOUT DETROL LA

INFORMATION ABOUT DETROL LA

BE-DRI

GENERIC NAME: Tolterodine tartrate

ACTION: Detrol helps urinary incontinence by relaxing the bladder muscles so that you do not feel a strong urge to urinate. Detrol LA is one of the drugs used frequently to treat urge incontinence.

Detrol LA is not an experimental drug.

DOSE: Detrol LA should be taken once a day. It is important to take the drug at the same time each day. We recommend that you take the drug at bedtime. The capsule should be taken by mouth with liquids.

MISSED DOSE: Detrol LA is an extended release capsule. This means that the drug is released over a 24-hour period. Therefore, if you forget to take the capsule, you can take it up to 12 hours after the time you usually take the drug.

SIDE EFFECTS: The most common side effects are dry mouth and constipation.
If you develop dry mouth, the following should be helpful:

- Chew sugar-free gum.
- Suck on sugar-free hard candy.
- Sip water, especially during meals to help swallow food.
- Use fluoride toothpaste to help prevent dental cavities.
- Avoid mouthwashes with alcohol. Try 1-teaspoon salt and 1-teaspoon baking soda in a quart of water as a mouthwash.
- Use an oral lubricant, available over-the-counter located near the toothpastes.

If you develop constipation, please ask the nurse for a list of suggestions.

Other less frequent side effects include headache, abdominal pain, dizziness, indigestion, blurred vision, dry eyes, sleepiness or fatigue. Please let us know if you experience any of these symptoms.

OTHER DRUGS: Due to the nature of the study protocol, if you must take any of the drugs listed on the following pages at the time that you are participating in the BE-DRI Study we need to know. Please call the study nurse before taking the drug.

If you have any questions or concerns, please call:

NAME: _____ **PHONE NUMBER:** _____

Need To Know Drugs Listed Alphabetically by Generic Name First

- Amitriptyline (**Elavil, Endep**)
- Amoxapine (**Asendin**)
- Belladonna alkaloids/Phenobarbital (**Donnatal**)
- Clidinium (**Quarzan**)
- Clomipramine (**Anafranil**)
- Desipramine (**Norpramin**, **Pertofrane**)
- Dicyclomine (**Bentyl**)
- Doxepin (**Adapin**, **Sinequan**)
- Duloxetine (**Cymbalta**)
- Glycopyrrolate Tablets (**Robinul, Robinul Forte**)
- Homatropine (**Homapin**)
- Hyoscyamine (**A-Spas S/L, Anaspaz, Cystospaz, Donnamar, ED-Spaz, Gastrosed, Hyco elixir, Hyosyne, Hysosol, Hyospaz, Levbid, Levsin, Levsinex Timecaps, Levsin/SL, Losamine, M**)
- Hyoscyamine sulfate (**Cystospaz-M**)
- Imipramine (**Janamine**, **Tofranil**)
- Imipramine Pamoate (**Tofranil PM**)
- Mepenzolate (**Cantil**)
- Nortriptyline (**Aventyl**, **Pamelor**)
- Oxybutynin (**Ditropan, Oxytrol patch**)
- Propantheline (**Pro-Banthine**)
- Propantheline Bromide (**Pro-Banthine**)
- Protriptyline (**Vivactil**)
- Tolterodine (**Detrol**)
- Trimipramine (**Surmontil**)

Need To Know Drugs Listed Alphabetically by Trade Name First

- **Adapin** (Doxepin)
- **Anafranil** (Clomipramine)
- **Anaspaz** (Hyoscyamine)
- **Asendin** (Amoxapine)
- **A-Spas S/L** (Hyoscyamine)
- **Aventyl** (Nortriptyline)
- **Bentyl** (Dicyclomine)
- **Cantil** (Mepenzolate)
- **Cymbalta** (Duloxetine)
- **Cystospaz,** (Hyoscyamine)
- **Cystospaz-M** (Hyoscyamine sulfate)
- **Detrol** (Tolterodine)
- **Ditropan** (Oxybutynin)
- **Donnamar** (Hyoscyamine)
- **Donnatal** (Belladonna alkaloids/Phenobarbital)
- **ED-Spaz** (Hyoscyamine)
- **Elavil** (Amitriptyline)
- **Endep** (Amitriptyline)
- **Gastrosed** (Hyoscyamine)
- **Homapin** (Homatropine)
- **Hyco elixir** (Hyoscyamine)
- **Hyospaz** (Hyoscyamine)
- **Hyosyne** (Hyoscyamine)
- **Hysosol** (Hyoscyamine)
- **Janamine** (Imipramine)
- **Levbid** (Hyoscyamine)
- **Levsin** (Hyoscyamine)
- **Levsin/SL** (Hyoscyamine)
- **Levsinex Timecaps** (Hyoscyamine)
- **Losamine, M** (Hyoscyamine)
- **Norpramin**, (Desipramine)
- **Oxytrol patch** (Oxybutynin)
- **Pamelor** (Nortriptyline)
- **Pertofrane** (Desipramine)
- **Pro-Banthine** (Propantheline)
- **Pro-Banthine** (Propantheline Bromide)
- **Quarzan** (Clidinium)
- **Robinul** (Glycopyrrolate Tablets)
- **Robinul Forte** (Glycopyrrolate Tablets)
- **Sinequan** (Doxepin)
- **Surmontil** (Trimipramine)
- **Tofranil** (Imipramine)
- **Tofranil PM** (Imipramine Pamoate)
- **Vivactil** (Protriptyline)

ATTACHMENT B

DRY MOUTH HANDOUT

DRY MOUTH

If you develop dry mouth, the following should be helpful with symptoms:

1. Chew sugar-free gum.
2. Suck on sugar-free hard candy.
3. Sip on water, especially during meals to help swallow food.
4. Use fluoride toothpaste to help prevent dental cavities.
5. Avoid mouthwashes with alcohol.
Try 1 tsp salt and 1 tsp baking soda in a quart of water as a mouthwash.
6. Use an oral lubricant, available over-the-counter located near the toothpastes.

ATTACHMENT C

CONSTIPATION HANDOUT

CONSTIPATION

BE-DRI

Constipation is defined as the passage of hard stools less than three times a week or difficulty passing stools. Contrary to popular belief, it is not necessary to have a bowel movement every day. "Normal" bowel movements vary from person to person. Many things, such as not drinking enough fluids, lack of physical activity, a diet low in fiber, and even certain medicines may contribute to the problem. Sometimes, but not often, constipation may be due to serious medical problems. If you become constipated, it is wise to speak to your physician about the problem so that serious illness can be ruled out.

Regular use of a laxative, especially for a long time, can actually cause constipation rather than relieve it. When you use laxatives regularly, you interrupt the body's normal way of emptying waste. Overuse of mineral oil may reduce the absorption of certain vitamins (A, D, E, and K). Some laxatives can interfere with the medications your doctor has prescribed for you. When you stop using laxatives after a long period of time, you may find that you cannot have a bowel movement without them. However, it is still possible to break this cycle.

Although many laxatives may be used on occasion, never use them for more than a week, unless your doctor prescribes them. Instead, try to prevent or relieve constipation by using more natural measures:

1. **Drink enough fluids** such as water, or other caffeine free, non-alcoholic fluids: the equivalent of six to eight glasses a day -(unless your doctor instructs you otherwise).

2. **Increase fiber in your diet**. The average American diet contains 10-15 grams of fiber a day. The recommended intake of fiber is 20-25 grams per day. Good sources include bran and whole-grain cereals and breads, fruit, fresh vegetables, and beans. In order to avoid feeling "bloated" or "gassy," slowly increase dietary fiber over several weeks. Prune juice, apples, and pears seem to work particularly well for some people.

3. **Exercise regularly**. A daily walk for at least 15 minutes (more if you can) will help not only your bowels, but also your heart, muscles, and over-all attitude toward life. If you are not exercising regularly, be sure to check with your doctor before beginning a new program.

4. **Try to develop a regular bowel habit**, such as attempting to have a bowel movement after breakfast or dinner each day. Some people prefer to have their bowel movements only at home, but delaying a bowel movement can actually lead to constipation. Response to the natural urge as quickly as possible even if you are away from home.

5. **Take an over-the-counter psyllium-based fiber supplement**. These are not laxatives, but they increase the amount of the water content in your stool, making it softer and easier to pass. These can be taken in pill or capsule form or as granules mixed in water or juice. They are taken on a daily basis to prevent constipation. Be sure to include additional water in your diet if you take extra fiber: these liquids will become part of your elimination in your stool instead of your urine.

6. **Avoid powerful laxatives** containing cascara, senna, or sennoside, unless prescribed by your doctor. When you do need a laxative, ask your doctor what he or she recommends. Docusate (a stool softener), Milk of Magnesia, glycerin suppositories, or mineral oil are common choices. Be sure you do not use them for longer than a week. If you are currently "hooked" on laxatives, you may need to wean yourself off over a period of several weeks. At the same time you should be careful to drink plenty of water, exercise regularly (both with your doctor's permission), and increase the fiber in your diet and/or include a fiber supplement (See 2 and 5 above).

7. **Please consult your doctor** if you have blood in your stool, unexplained weight loss, severe constipation, or a change in bowel habits. The constipation may be a sign of other health problems.

Provided courtesy of University of Alabama at Birmingham

ATTACHMENT D

FLUID MANAGEMENT HANDOUT

FLUID MANAGEMENT INSTRUCTIONS

- The average fluid intake for a healthy adult is considered to be 50 to 70 ounces of liquid each day. This means that each day you should consume the equivalent of 6 to 8 eight-ounce glasses of liquids (including any beverages and soups), much of which can be in the form of solid foods.

- This should produce a healthy 40-50 ounces of urine in 24 hours. If you voided much more than this volume on your diary, you may want to adjust your intake to produce more normal amounts of urine. People who work in hot climates or exercise heavily need more fluids because of loss through perspiration, but their urine output should still be approximately 40-50 ounces.

- Spread out your consumption of liquids rather than consuming a lot at one time, and try to avoid fluids within a few hours of going to bed. Don't drink fluids overnight.

- If your urine output is less than 40 ounces in 24 hours, and cannot be explained by losses due to urine leakage, you may need to drink more fluids.

ATTACHMENT E

APPOINTMENT LOG

BE-DRI

APPOINTMENT LOG

Name: _____

Visit 1: _____ Date _____ Time

Visit 2: _____ Date _____ Time

Visit 3: _____ Date _____ Time

Visit 4: _____ Date _____ Time

Visit 5: _____ Date _____ Time

If you have any questions, please call the study nurse:

Name: _____ **Phone Number:** _____

Please remember to bring your pill bottle and this Appointment Log to every visit.