

# **Protocol for Brain-Centered Therapy versus Medication for Urgency Urinary Incontinence An RCT: Hypnotherapy Or Pharmacotherapy**

**Acronym: Hyp-hOP**

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## Abbreviations

ACC	Anterior Cingulate Cortex
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
AI	Anterior Insula
ANCOVA	Analysis of covariance
BOLD	Brain oxygen level dependent
Botox	Onabotulinum toxinA
BPIC-SS	Bladder Pain/ Interstitial Cystitis Symptom Score
CD	Compact Disc
CTSC	Clinical Translational Science Center
Co-I	Co-Investigator
Co-PIs	Co-Primary Investigators
CRADI-8	Colorectal Anal Distress Inventory-8
CRF	Case report form
CTSC	Clinical Translational Science Center
Cystom.	Cystometrics
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
e.g.	example
Etc.	etcetera
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of view
f/u	Follow-up
H <sub>0</sub>	Null hypothesis
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research and Protections Office
Hyp-hOP	Hypnotherapy Or Pharmacotherapy: Acronym for Protocol for Brain-Centered Therapy versus Medication for Urgency Urinary Incontinence An RCT: Hypnotherapy Or Pharmacotherapy
Hz	hertz
IBS	Irritable bowel syndrome
IC	Interstitial Cystitis
ICI	International Consultation on Incontinence
ISI	Incontinence Severity Index
ID	Identifier/identification
i.e.	Id est=in other words
info	information
IRB	Institutional Review Board
ITT	Intention to treat
LA	Long Acting
MD	Medical doctor
mo	month
MOP	Manual of Procedures/ Manual of Operations

MPH	Master of Public Health
N	number
NA	Not applicable
NCCAM	National Center for Complementary and Alternative Medicine
NEX	Number of excitations
OAB	Overactive Bladder
OABq-SF	Overactive Bladder Questionnaire-Short Form
OFC	Orbital Frontal Cortex
PI	Primary Investigator
PISQ-12	Pelvic Organ Prolapse Incontinence Sexual Questionnaire-12 (Short form)
POP-Q	Pelvic Organ Prolapse Quantitation
PPBC	Patient Perception Bladder Condition
RCT	Randomized controlled trial
SAE	Serious Adverse Event
T1	Spin lattice relaxation time
T2	Spin spin relaxation time
TE	Echo time
TR	Repetition time
UNM	University of New Mexico
UNMH	University of New Mexico Hospitals
UTI	Urinary Tract Infection
UUI	Urgency Urinary Incontinence
VAS	Visual Analogue Scale
XR	Extended Release
yo	Years old
ZIP	Zero inflated poissons
μ	Mu; used in the text as 'mean'
μ <sub>h</sub>	Mean of hypnotherapy
μ <sub>m</sub>	Mean of medication

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## Précis

### Brain-Centered Therapy versus Medication for Urgency Urinary Incontinence--An RCT: Hypnotherapy or Pharmacotherapy

#### Study Goals & Brief Description:

##### Goals/Objectives:

Specific Aim (1) Determine whether a mind/body therapy (hypnotherapy) is at least as effective and durable in treating urgency urinary incontinence (UUI) as a non-mind/body treatment (pharmacotherapy)

*Hypothesis: Among patients with urgency urinary incontinence, hypnotherapy ameliorates abnormal perception of bladder distension outside the hypnotic state and thereby is at least as effective as pharmacotherapy in diminishing the symptoms of urgency and severity of incontinence*

Specific Aim (2) Determine whether hypnotherapy treatment of UUI (urgency urinary incontinence) is associated with greater modification of brain activation and connectivity on functional MRI than that which occurs following pharmacotherapy.

*Hypothesis 2.1. Patients with urgency urinary incontinence will exhibit increased activation within portions of the limbic cortex (anterior cingulate cortex and insula) during bladder distension relative to healthy controls. Patients will also exhibit an abnormal pattern of functional connectivity within the limbic system.*

*Hypothesis 2.2. Among patients with urgency incontinence, hypnotherapy will decrease hyper-activation of the limbic cortex in response to bladder distension and/or modulate functional connectivity within the limbic system. Moreover, normalization of hyper-activation and connectivity will be greater in hypnotherapy compared to pharmacotherapy.*

#### Brief Description: Design, Outcome, Interventions, Duration, Sample Size and Population:

This study includes

1. A single-blinded, randomized controlled trial (RCT) based on a non-inferiority design which compares hypnotherapy to pharmacotherapy in treating UUI
  - Urge incontinent women (N=152) will be randomized to hypnotherapy or pharmacotherapy and evaluated at months 2, 6 & 12; study duration is thus 1 year. UUI subjects will be stratified for UUI severity and fMRI performance.
  - The primary objective will be to compare group change in UUI episodes at 2 month follow-up.
  - Secondary objectives will be to compare group change in UUI episodes at 6 & 12 months, other voiding diary parameters (urinary frequency, pad counts, cure and “durable cure”), and change in the OAB-qSF and other questionnaires (see 1.2) at 2, 6 & 12 months.
2. Both a cross sectional study and RCT which will compare pre-treatment brain function in subjects with UUI to controls and compare the effect of hypnotherapy and pharmacotherapy on brain function in patients with UUI.
  - Up to eighty women (of the planned 152) with UUI will be recruited in order to obtain up to sixty analyzable fMRI datasets. Up to 30-35 normative controls will be recruited in order to achieve 25-30 analyzable fMRI datasets from normative controls. fMRI datasets from UUI patients will be compared to fMRI datasets from normative controls. The normative controls will be involved in the study for a month or less.
  - In addition, the same, up to 80, UUI subjects will also undergo fMRI analysis after receiving treatment (hypnotherapy or pharmacotherapy) for two months. Post treatment fMRI results from UUI subjects will be compared to their baseline images. These UUI subjects will complete the fMRI portion of the trial after being “on study” for 2 months but will continue to have follow up for the RCT analysis for one year (See #1 above)
  - Measured outcomes will be differences in baseline brain activation and connectivity in UUI subjects compared to controls as well as differences in treatment effect on brain activation and connectivity in subjects receiving pharmacotherapy compared to those receiving hypnotherapy



## **1. Study Objectives**

### **1.1 Primary Objective:**

- 1.1.1. To determine whether a mind/body therapy (hypnotherapy) is at least as effective and durable in treating urgency urinary incontinence (UUI) as a non-mind/body treatment (pharmacotherapy), comparing between group changes in UUI episodes recorded on voiding diaries at 2 months based on a non-inferiority design.
- 1.1.2. To determine whether hypnotherapy treatment of UUI (urgency urinary incontinence) is associated with greater modification of brain activation and connectivity on functional MRI than that which occurs following pharmacotherapy

### **1.2 Secondary Objectives:**

- 1.2.1 To determine whether a mind/body therapy (hypnotherapy) is at least as effective and durable, in treating urgency urinary incontinence (UUI) as a non-mind/body treatment (pharmacotherapy).
  - 1.2.1.1.1 We will compare differences in UUI “cure” (defined as complete resolution of UUI on voiding diaries) separately evaluating 2, 6 and 12 month results (i.e. “cure” at 2, 6 and 12 months).
  - 1.2.1.1.2 We will also compare between group differences in “durable cure” (defined as complete resolution of UUI on all voiding diaries collected at 2, 6 & 12 months).
  - 1.2.1.1.3 We will compare change in UUI episodes at 2, 6 & 12 months evaluating change in urinary frequency and pad counts recorded on voiding diaries.
  - 1.2.1.1.4 We will compare between group differences in change in questionnaire scores (OAB-q SF, ISI, Global questionnaires and PISQ-12 scores) and between group differences in the post-treatment Expectation question at 2, 6 & 12 months.
- 1.2.2 Additionally, we will evaluate the baseline occurrence of concomitant syndromes such as irritable bowel and painful bladder syndrome in this population of women with UUI based on the medical history, CRADI-8, IBS Module, and IC and VAS pain questionnaires. We will explore whether there are differences in bowel or IC symptoms following treatment if there are sufficient numbers of women with bowel or IC problems at baseline.
- 1.2.3 To confirm differences in brain activation and connectivity on functional MRI in UUI subjects compared to normative controls.

## 2. Background and Rationale

### 2.1 Background

Urgency urinary incontinence (urgency associated with involuntary urine loss, or UUI)<sup>38</sup> affects millions of women daily and can impair quality of life more than diabetes. Twice as common in women, urgency incontinence increases with age and afflicts 24% of women  $\geq 40$  years old.<sup>16</sup> It is associated with nursing home placement in the elderly and its stigma results in social isolation, depression and decreased work productivity in younger women.<sup>16,41,52,59,69</sup> Urgency incontinence burden will increase as the U.S. population ages and will consume 76 billion dollars in 2015 and 86 billion dollars by 2020.<sup>32</sup> Despite the magnitude of this problem, medications, a cornerstone of treatment, are only 15% more effective than placebo with little evidence of durability beyond 12 weeks.<sup>38,54</sup> Medications are poorly tolerated, with compliance as low as 45% at 1 month and 13% at 1 year.<sup>21</sup> Patients who continue medications are unlikely to be cured and must bear the cost of chronic drug therapy.<sup>54</sup> In 2000, the U.S. spent \$1.2 billion for these medications.<sup>38</sup> The cost will continue to rise as the number of Americans most at risk for incontinence, those older than 65, increases an additional 21% by 2015.

While pharmacotherapy of urgency incontinence has focused the diminishing motor innervation of the bladder by blockade of the peripheral parasympathetic system, new paradigms point to the alternative of focusing treatment on the brain. Treatment based on recognition of urgency incontinence as a functional disorder provides an alternative to continued costly reliance on pharmacotherapy. Current knowledge suggests UUI pathogenesis is similar to other functional disorders such as irritable bowel syndrome (IBS) and fibromyalgia. Advances in brain imaging suggest that increased perceptual awareness, or hyper-vigilance, is likely the cause of functional disorders.<sup>6,45,74</sup> Specifically, magnetic resonance imaging (MRI) of the brain has shown that women with urgency incontinence manifest abnormal activation of the limbic cortex, the portion of the brain that integrates emotional context with stimuli arising within the body (interoception).<sup>20,27,33,36,71</sup> Connectivity between the limbic cortex and other portions of the brain may also be altered in patients with urgency incontinence. No urgency incontinence treatment has specifically targeted brain activation and connectivity as a means of controlling symptoms nor has any attempt been made to assess changes in abnormal brain activation or connectivity following treatment. The effects of mind/body therapies on brain function have only been studied during or immediately after treatment.<sup>48</sup> This proposal will be the first work to assess whether mind/body therapy of a functional disorder is accompanied by persistent changes in brain function. Hypnotherapy, a mind/body therapy that can be administered in a standardized and reproducible fashion, is the best candidate for assessing these changes.

Hypnosis can profoundly alter sensory awareness and cognitive processing in response to external stimuli.<sup>24</sup> It promotes “dissociation from painful experience and distress via hypnotic induction” and modulates activation of the limbic cortex in response to pain and conflict resolution.<sup>28</sup> Hypnotherapy has been used to successfully treat other functional disorders, with subjects experiencing lasting decrease in symptoms outside the hypnotic state.<sup>60,42</sup> These successes are best characterized in the treatment of irritable bowel syndrome (IBS), a functional gastrointestinal disorder closely analogous to urgency incontinence.<sup>34,47</sup> No work has yet addressed whether persistent change in brain activity or connectivity underlies this post-hypnotic clinical improvement.

Our long term goal is to shift the focus of UUI treatment towards the brain and away from the peripheral nervous system. The objective here, in pursuit of that goal, is to determine whether hypnotherapy can be at least as effective in treating UUI as current pharmacologic therapy. Our central hypothesis is that hypnotherapy can be used to modulate neurologic interactions between the brain and bladder, providing effective UUI treatment. Recent work using functional magnetic resonance imaging (MRI) of the brain has better delineated the abnormal neurologic interactions that could be targeted for treatment of UUI, specifically, the accentuated neural responses to afferent signals from visceral organs that are the basis for hyper-vigilance.<sup>6,12,23</sup> Mind/body, specifically hypnotherapy, treatment of UUI offers the hope of targeting this hyper-vigilance and redirecting focus of UUI treatment to the brain. Hypnotherapy has successfully treated other functional disorders.<sup>6</sup> One case series and our own pilot randomized controlled trial indicate that hypnotherapy can be a well-tolerated, effective treatment for UUI.<sup>29</sup> Neurophysiologic models link the effects of hypnotherapy to altered activation of the limbic (emotional) brain and its connections with the executive control portions of the brain.<sup>25,26</sup> This process modulates subject attention and offers the means to counterbalance the effects of hyper-vigilance.<sup>26</sup> The rationale for our proposal is based on this prior work which has shown that brain activation is abnormal in subjects with UUI, that UUI may respond to hypnotherapy, and that hypnotherapy targets these sites of abnormal brain activation. Proof that hypnotherapy provides durable relief from UUI would change the focus of UUI treatment and would demonstrate

the physiologic basis for the use of a mind/body therapy to treat UUI, a functional disorder that affects a large segment of the population. We will test our central hypothesis with the study goals described previously.

## 2.2 Rationale

For the RCT: Specific Aim 1) Pharmacotherapy for urgency incontinence targets bladder receptors. It has had uneven therapeutic success due to side effects that have deterred long term use.<sup>24,66,38</sup> The objective of this aim is to change the target of urgency incontinence therapy to the brain using hypnotherapy to provide a treatment which is as effective and durable as the standard treatment, pharmacotherapy. To attain this objective, we will test our working hypothesis that the central abnormality in urgency incontinence is an altered perception of bladder distension and that hypnotherapy more directly affects this abnormality than medications, resulting in greater improvement in urinary urgency and incontinence. Our approach randomizes women to active interventions for 8 weeks; 8 weeks of hypnotherapy sessions vs. 8 weeks of pharmacotherapy with counseling sessions. Pharmacotherapy treatments will utilize standard anticholinergic medications, long-acting Tolterodine or Oxybutynin. Regarding the choice of anti-cholinergics, meta-analyses conclude that no one drug has proven superior in treating urgency incontinence but that, extended release formulations of medications are more effective than immediate release.<sup>38</sup> We will compare change in improvement in voiding diaries and validated questionnaires following both treatments. We will follow subjects at 2 months, then at 6 and 12 months. The 8 weeks of active interventions will be followed by recommendations for self-hypnosis and/or hypnosis audiofile use or continued medication use for 12 months. The rationale for this aim is to demonstrate that hypnotherapy targeting hyper-vigilance improves urinary continence as well as does pharmacotherapy. When the studies proposed in Aim #1 have been completed, we expect that the results will redirect the focus of incontinence treatment towards mind-based therapy and foster additional trials of this therapy for other functional disorders. For the fMRI: Specific Aim 2): Current knowledge suggests urgency incontinence pathogenesis is similar to other functional disorders such as IBS, representing a manifestation of "hyper-vigilance" to normal body sensations.<sup>6,55,75</sup> The objective of this aim is to demonstrate that hypnotherapy results in sustained post-therapy amelioration of abnormal limbic cortical function that is the physiologic correlate of this abnormal perceptual state present in patients with urgency incontinence on fMRI. Among patients with functional disorders abnormal activity within the limbic cortex involves the insula and anterior cingulate cortex.<sup>6,23,40,61</sup> Conceptually, the insula can be considered the sensory cortex for physiologic conditions and the anterior cingulate cortex the limbic behavioral motor cortex.<sup>27</sup> As the latter, anterior cingulate cortex activation is associated with the emotional response to discomfort and is activated during expectation of unpleasant events.<sup>75</sup> Patients with functional disorders manifest both abnormal activation of the limbic cortex and abnormal connectivity between these structures and other sites in the brain.<sup>62,68</sup> This connectivity is complex and analyses of its structure have varied between investigators and between specific functional disorders.<sup>56,12,70</sup> In most studies controls and subjects with functional disorders have displayed differences in connectivity between the limbic cortex and sites in the central executive network (e.g. prefrontal cortex).<sup>45,56,72</sup>

Hypnotherapy offers a mechanism to sustain that effect in order to provide clinically useful therapy. The hypnotic state results in functional changes in the limbic cortex. It has been shown to decrease anterior cingulate cortex activation in response to acute pain and in response to conflict monitoring.<sup>63,73</sup> The interaction between the anterior cingulate cortex and the other portions of the brain during hypnosis, however, is not constant across all settings. Connectivity with the prefrontal and frontal cortex may increase when pain is suppressed by hypnosis and diminish when conflict monitoring is suppressed by hypnosis.<sup>24,25,53,60</sup> Furthermore, the anterior cingulate cortex is not the sole target in the limbic cortex for mind/body therapies. It appears to be an important nexus for acute stimuli but chronic symptoms may be mediated elsewhere.<sup>31</sup> Treatment of chronic pain with both hypnosis and acupuncture is associated more strongly with decreased activation of the insula and alterations of its connectivity to other sites including the central executive network.<sup>2,5,48</sup> Modulation of activity in these sites has been associated with acute amelioration of chronic pain.<sup>69</sup> Alteration of insula connectivity persists for the first hour following therapy and may be important in achieving a sustained treatment effect.

Our working hypothesis is that among patients with urgency incontinence hypnotherapy causes sustained decreases in abnormal evoked activation of the limbic cortex in response to bladder distension and/or modulates abnormal intrinsic activity (functional connectivity) in these same areas. We also predict that this normalization of evoked activation and functional connectivity will be greater than that seen with

pharmacotherapy. Our approach will be to evaluate evoked brain activation and functional brain connectivity on fMRI in normative subjects and in urge incontinent subjects, the latter pre and post treatment after randomization to drug or hypnotherapy. The rationale for this approach is to demonstrate that hypnotherapy treatment of urgency incontinence ameliorates limbic system activity and abnormal resting connectivity associated hyper-vigilance. Demonstration that this therapeutic effect is sustained outside the hypnotic state would be the initial exploration of brain plasticity in response to mind/body therapy. The expected outcome of this innovative proposal would be the first demonstration of the physiologic correlate of successful mind/body treatment of a functional disorder.

### 3. Study Design

#### Brief Description:

This study includes

1. A single-blinded, randomized controlled trial (RCT) based on a non-inferiority design which compares hypnotherapy to pharmacotherapy in treating UUI.
  - Urge incontinent women (N=152) will be randomized to hypnotherapy or pharmacotherapy and evaluated at months 2, 6 & 12
2. Both a cross sectional study and RCT which will evaluate up to 80 of these women with UUI.
  - These women will undergo fMRI before treatment and their baseline imaging results will be compared to normative controls.
  - In addition, the UUI subjects participating in the fMRI will undergo imaging after treatment. The images of UUI subjects following treatment will be compared to their baseline images.

#### Outcomes:

Primary Outcomes:

1. Between group differences in change in UUI episodes for Specific Aim 1 at 2 month follow-up based on 3 day voiding diaries
2. Between group differences in change in activation of limbic cortex and brain connectivity following treatment for Specific Aim 2

Secondary Outcomes:

1. Between group differences in change in UUI episodes for Specific Aim 1 from baseline to follow-up at both 6 and 12 months based on 3 day voiding diaries.
2. Between group differences in change in pad counts, voiding frequency and cure (resolution) of UUI on voiding diary for Specific Aim 1 at 2, 6 and 12 month follow-up as well as “durable cure” (resolution of UUI on all follow-up diaries at 2, 6 & 12 months)
3. Between group differences in the post-treatment expectation question and between group differences in questionnaire change scores (the OAB-qSF, ISI, PISQ-12, Global questionnaire, CRADI-8, IBS Module, IC questionnaire) for Specific Aim 1 at 2, 6 and 12 month follow-up
4. Baseline differences in activation of the limbic cortex and brain connectivity in women with UUI compared to normative controls for Specific Aim 2

#### Overview:

Women with UUI who meet inclusion criteria and who choose to participate in the study will be enrolled at the University of New Mexico Urogynecology Clinic. We will screen subjects for study entry as we always do clinically, based on voiding diaries to ensure that subjects have UUI (and not other types of incontinence) and with a screening questionnaire, the OAB Awareness tool. Subjects will be randomized to treatment with either: 1) Pharmacotherapy (a standard therapy for UUI) and conventional behavioral therapy or 2) Hypnotherapy and conventional behavioral therapy. All subjects will give signed informed consent prior to study treatment. Approximately 152 women will be randomized to hypnotherapy or to pharmacotherapy with approximately half in each group. UUI subjects will be informed that study participation will be approximately 1 year; Measurements will be performed prior to treatment, following completion of treatment visits (treatment visits are performed over 8 weeks), and again at 6 and 12 months. The latter visits at 6 and 12 months do not necessarily require in-person

study visits and may be performed via phone and mail. The primary analysis of the RCT will be performed as an intention to treat analysis. A secondary analysis will be performed as a per protocol analysis.

A subset of subjects with UUI (up to 80) in both treatment groups will have brain fMRIs performed at baseline and follow-up at the Mind Research Network. In addition, 30-35 normative controls will also undergo an fMRI at the Mind Research Network to compare fMRI in affected women versus controls. Subjects will give signed informed consent prior to study participation

#### Randomization to treatment for RCT:

##### *A. Randomization to treatment*

Study participants will be randomized to either pharmacotherapy or hypnotherapy groups using a computer-generated randomization scheme in varying permuted block sizes of 4-8 which will be stratified for fMRI performance and UUI severity (< 4 UUI episodes vs. ≥ 4 UUI episodes on 3 day voiding diaries) to ensure relatively equal numbers in both treatment groups. Group assignments will be placed in opaque, sealed envelopes by an individual otherwise unassociated with the study. The envelopes will be opened and subjects will be randomized only after subjects have signed informed consent and answered baseline questions and questionnaires. Investigators involved in analyzing fMRIs, investigators participating in the RCT, study personnel performing data entry and the study statistician will be blinded to knowledge of subjects' treatment groups. Investigator blinding will only be breached if a subject suffers an unexpected clinical event and investigator knowledge of the subject's treatment is essential to providing standard of care. Subjects cannot be blinded to treatment interventions as it will be obvious to them whether or not they are undergoing hypnotherapy or taking medications.

#### Visits for Study: (Refer to Flow Diagrams at end of this section)

##### *A. UUI STUDY SUBJECTS:*

**Screening:** Subjects in the UNMH Urogynecology clinics with UUI who qualify for study entry will be asked whether they are interested in study participation. These subjects will be assured that declining study participation will not affect their clinical care. In addition, women with UUI who contact the UNMH Ob-Gyn research division expressing interest in study participation will have the study explained to them and follow the same procedures as UNMH subjects (see following). Potential subjects will be given a copy of the study consent for their review. Those who are interested will be administered the OAB Awareness tool,<sup>18</sup> a validated measure which screens for presence of OAB, to screen whether or not they are candidates for the study. They will also be instructed how to keep a voiding diary. If they ultimately choose to participate in the study, they will be asked to bring the diary with them for Visit 1 (below). The patient will be given the option to schedule Study Visit 1 or given the option to contact the study coordinator to schedule Study Visit 1 at a later date if they are uncertain regarding study participation.

**Visit 1** (At study entry): All subjects; (1) Will return voiding diaries (which will be reviewed by the study coordinator for completeness and UUI frequency) & instruction regarding voiding diaries will be reiterated & arrangements made for return of future voiding diaries (2) Will be administered the OABq-SF questionnaire,<sup>15</sup> the Incontinence Severity Index (ISI), and the Patient Perception of Bladder Condition (PPBC).<sup>85</sup> (see questionnaires attached). The OABq-SF questionnaire is a condition specific validated questionnaire developed to quantitate OAB symptoms and the PPBC is a validated global questionnaire regarding subjects' impression of the severity of their urinary condition.<sup>84</sup> The ISI is a commonly used, validated 2 item questionnaire which adds another dimension to the outcomes, a description of UUI severity and is an accepted outcome measure in the 2012 AHRQ summary of nonsurgical treatments of urinary incontinence.<sup>84</sup> If subjects are willing, they will also answer a condition-specific validated measure of sexual function, the PISQ-12.<sup>64,65,66</sup> Urinary incontinence has been found to adversely affect sexual function and many studies have reported upon its improvement following therapy.<sup>67,68,16</sup> (3) Answer demographic questions and questions about their past medical history. Subjects will also be administered the Colorectal Anal Distress Inventory 8 (CRADI-8) subscale of the PFDI-20 (which has been validated in women with bowel symptoms and pelvic floor disorders),<sup>87</sup> the Rome III IBS Module, and the Painful Bladder Interstitial Cystitis Symptom Score (PBIC-SS)<sup>86</sup> and Pain Visual Analogue Scale,<sup>37</sup> as irritable bowel (IBS) and painful bladder (Interstitial Cystitis) syndromes are associated with UUI. IBS and IC may be

important covariates in treatment success and have responded to other UUI treatments (4) Will have already undergone a pelvic examination which includes the Pelvic Organ Prolapse Quantitation (POP-Q) Exam during their routine clinical evaluation within the last year; if they have not, however, they will undergo a POP-Q exam. The POP-Q is a validated examination recommended by the International Continence Society to standardize quantitation of subjects' prolapse<sup>9</sup> (5) Subjects will have cystometry scheduled as this is part of clinical care to help distinguish between the different types of incontinence. This is a test where subjects have a catheter placed in the bladder, the bladder is filled with sterile fluid and bladder volumes at which sensations of urgency and desire to void occur are recorded. Subjects who have undergone formal UDS and whose UDS results are available, do not have to have cystometry repeated unless they choose to participate in the fMRI study. (6) Subjects who are willing to undergo fMRI and are free from MRI contraindications will be informed of the date/time of the fMRI visit or their contact information will be obtained. They will be contacted regarding the fMRI date/time before Visit 3 (7) Behavioral interventions, a standard treatment for urgency incontinence, will be discussed with all subjects and a hand-out will be given to all subjects and arrangements for future contact with subjects will be made.

*Visit 2:* Cystometry will be performed (see #5 above, Visit 1) Cystometry is a test where subjects have a catheter placed in their bladder, the bladder is filled with sterile fluid and bladder volumes at which sensations of increasing urge to void are recorded. It is part of clinical care to help distinguish between the different types of incontinence. Subjects will be treated with prophylactic antibiotics the day of cystometric testing after documenting absence of allergies to the antibiotics prescribed. Prior to cystometry the subjects will have a urine pregnancy test (if they are premenopausal and have not had a hysterectomy or permanent sterilization) and urine dipstick performed to rule out a urinary tract infection. While the bladder catheter is still in place, subjects may have urine and vaginal swab samples collected and stored for possible future analysis (For example, urine may be analyzed for biomarkers and microbiome analysis). Those who will undergo fMRI will also undergo a brief simulation of the procedure to be performed in the fMRI; their bladders will be filled and emptied and they will rate their urge to void (from 0-10) while this occurs. This will be done in order to decrease anxiety regarding the procedure while in the fMRI scanner. Subjects may undergo hypnotic susceptibility testing (using the validated Stanford C Hypnotic Susceptibility Test) at this time or any time before their 1<sup>st</sup> intervention treatment.

*Visit 3 for fMRI subjects:* Up to eighty of the UUI subjects (approximately half from the hypnotherapy group and half from the pharmacotherapy group) willing to have an fMRI and without contraindications to fMRI will participate in the fMRI portion of the study and will return for their baseline fMRI. Urine dipstick testing and pregnancy testing (in women who are premenopausal and without a history of a hysterectomy or permanent sterilization) will be performed: subjects who are pregnant or who have a urinary tract infection may not undergo fMRI testing. fMRI subjects will be pretreated with prophylactic antibiotics, will have a bladder catheter placed and will be asked to a) concentrate on a picture placed before them while they have the MRI performed b) they will next have their bladders filled with sterile fluid and be asked to rate the degree of bladder discomfort or "urge to void" experienced during bladder filling c) they will then have the catheters removed, the amount of urine voided will be measured and subjects will be discharged to home and given instructions to contact the study personnel if questions or problems arise.

*The subjects will be randomized to treatment interventions and contacted by the study personnel and arrangements made for their interventions, which must begin within one month. Subjects will be administered the Patient Expectation question.*

*Visits Overview:* Hypnotherapy subjects will have a total of 8 hypnotherapy sessions scheduled over 8 weeks and Conventional pharmacotherapy subjects will have a total of 8 visits scheduled over 8 weeks with the medication counselor (see the following)

*Visit for Hypnotherapy Subjects: Visit 3 (for subjects who did not undergo fMRI) Visit 4 (for subjects who did undergo fMRI): Hypnotherapy Subject Visits 3-10 for those who did not undergo fMRI, Visits 4-11 for those who did undergo fMRI-- 8 hypnotherapy sessions over 8 weeks-- Hypnotherapy sessions:* Subjects assigned to hypnotherapy will be scheduled for these visits which will be performed by a certified clinical hypnotherapist, other than Dr. Robert Sapient. The hypnotherapists will be supervised by Dr. Robert Sapient, a certified hypnotherapist and Board Certified Pediatric Emergency Medicine physician and UNMH faculty member. The

subjects will be informed that the sessions will be audio-recorded and one or more sessions will be reviewed by study personnel to ensure that the hypnotherapist administers the hypnotherapy session in a standardized fashion. Recordings will be stored on the research computer and access to these recordings will be available to assigned research personnel only. All recordings will be stored for approximately 7 years, in the same fashion as other data, and then will be destroyed. The hypnotherapists have been instructed to not use the patients' name or any other identifiers during the recorded session. The subjects will undergo 8 hypnotherapy sessions over 8 weeks. Sessions will last approximately 60 minutes. Session #1: The hypnotherapist will explain hypnotherapeutic principles; subjects will inform the hypnotherapist regarding any phobias or fears (so that these triggers will be avoided). Subjects will undergo their 1<sup>st</sup> hypnotherapy session and hypnosis will then be terminated. Session #2: address emotions around UUI and life impact, visualize pelvic floor exercise mechanics, and undergo their 2<sup>nd</sup> hypnotherapy session followed by termination of hypnosis. Subjects will receive a CD or be instructed how to download a digital recording (for use on a digital device) specially prepared for them to for home practice of hypnotherapy sessions. This will occur at either their 2<sup>nd</sup> or 3<sup>rd</sup> hypnotherapy session; they will be instructed NOT to listen to the hypnotherapy CD/digital recording while driving and encouraged to listen to the CD/digital recording daily and record the home use of their CD/digital recording. Session #3,4,5,6,7; same as session 3. Session #8: same as previous sessions. In addition, the subjects will be counseled to expect occasional and temporary setbacks in their bladder symptoms and the hypnotherapist and subject will discuss how to cope with these setbacks.

*Pharmacotherapy Visit 3-10 for subjects who did not undergo fMRI, Visits 4-11 for those who did undergo fMRI ---8 medication counseling sessions over 8 weeks-- Medication Counseling Session:* Subjects assigned to pharmacotherapy (medications) will be scheduled for these visits which will be performed by trained personnel. The subjects will be informed that several or all sessions will be audio-recorded and one or more sessions will be reviewed by study personnel to ensure that the medication counselor administers the sessions in a standardized fashion. Recordings will be stored on the research computer and access to these recordings will be available to assigned research personnel only. All recordings will be stored for approximately 7 years, in the same fashion as other data, and then will be destroyed. The medication counselors have been instructed to not use the patients' name or any other identifiers during the recorded session. Subjects will be scheduled for in person visits with the medication counselor who will review medications and their side effects. However, if subjects state these in person visits are overly burdensome, these visits may occur via phone as long as the patient comes in for at least 2 of the subsequent visits for pill dispensation which should occur midway and at the end of the 8 sessions. These sessions will take as long as required/desired for subjects to feel that they have received adequate instruction/counseling. Discussion of strategies to cope with their bladder symptoms will occur. The expected side effects of medications (such as dry mouth, constipation) will be discussed and strategies to cope with side effects will also occur. It is expected that these sessions will take approximately 20-60 minutes, depending on the subjects' needs. The medication may be changed if the patient complains of side-effects from the initial anti-cholinergic or perceives that her response in UUI treatment is inadequate; a different anti-cholinergic may be given to the patient if she requests a different UUI medication. The study will use either of two standard, long acting anti-cholinergic medications and dosages (Long acting Tolterodine 4mg/day or Extended Release Oxybutynin 10 mg/day). Initial medication use will usually be Oxybutynin 10 mg/day but will depend on the patient history (for example those who have used Oxybutynin unsuccessfully will be given Tolterodine and vice versa). A recent AHRQ meta-analysis found that there was no difference in effectiveness or side-effects between the available anti-cholinergics used to treat UUI as long as the medications were extended release formulations, such as those used in this study.<sup>38</sup>

*Visit 12—follow-up fMRI testing (for the fMRI group):* Follow-up fMRI will be performed on the subjects who had baseline fMRIs performed. These will be performed in the same fashion as described in Visit #3. In addition, patients may have urine and vaginal swab samples collected and stored for possible future analysis (For example, urine may be analyzed for biomarkers).

*Final visit 11 (for those who did not undergo fMRIs) and Final visit 13 (for those who did undergo fMRI):* The final study visit will be scheduled at the end of the hypnotherapy or medication counseling sessions, approximately 8-12 weeks after study entry. Those who are in the subgroup who have undergone prior fMRI testing will have it performed at this session. At the final study visit, subjects will 1) be administered the OABq-SF, ISI, the PPBC, CRADI-8, IBS Module and IC questionnaires, PISQ-12 and answer the question regarding

how well the therapy met their expectations for treatment. Their compliance with medications or home practice of hypnotherapy will be documented 2) They will return their follow-up voiding diary 3) receive patient incentives for the time and inconvenience they have experienced from study participation. In addition, patients may have urine and vaginal swab samples collected and stored for possible future analysis (For example, urine may be analyzed for biomarkers).

*Length of visits:* Each hypnotherapy session will last approximately 60 minutes, each pharmacotherapy visit will take approximately 20-60 minutes, and each Brain fMRI visit will last approximately 60-120 minutes. The 6 and 12 month visits may be conducted via phone or mail, if the subject desires, in order to decrease subject inconvenience.

#### ***B. NORMATIVE CONTROLS PARTICIPATING IN ONLY THE FMRI STUDY:***

In addition to the UUI study subjects described previously, we will also enroll a group of women without UUI and OAB symptoms (and with OAB Awareness Tool screening questionnaire scores < 8). This normative group (approximately 30-35 subjects) will keep voiding diaries, answer questionnaires, and undergo urine pregnancy and dipstick testing and cystometric testing and receive prophylactic antibiotics (as described previously) followed by performance of a Brain MRI in order to compare baseline fMRIs in women with and without UUI.

*Screening:* FMRI portion of the study explained to subject, including the cystometry and fMRI procedures. Subject administered OAB Awareness tool and fMRI eligibility assessed. Subject given voiding diary instructions. Subject given copy of consent and either has visit scheduled to sign consent after subject has time to consider whether she wants to participate in the study. If subject states she is certain that she wants to participate, she has the option of signing the consent at this time. If the consent is signed, then the subject is administered the medical history and demographic forms. If subject states at this visit that she would like to participate in the study, appointments are scheduled for the cystometry and fMRI and arrangements are made for the patient to receive prophylactic antibiotics prior to the bladder catheterizations. If patient is uncertain whether she wants to participate, the research coordinator's contact information is given to the subject.

*Visit 1:* Subjects return for the visit with the voiding diary and study eligibility is re-confirmed. The consent is signed, if this has not happened previously. The medical history and demographics forms are administered. POP-Q exam is performed if it has not been performed in the last year. Cystometry is explained to the subject once more. Urine pregnancy test is performed (if patient is premenopausal and has not had a hysterectomy or permanent sterilization procedure) and urine screen for UTI performed. Cystometry is performed as previously described in Visit #2 for the UUI subjects. The subjects will also have simulation of the procedure to be performed in the fMRI. Patients will have urine and vaginal swab samples collected and stored for possible future analysis (For example, urine may be analyzed for biomarkers and microbiome analysis). Future fMRI appointment is confirmed.

*Visit 2:* Urine pregnancy test performed (if patient is premenopausal and has not had hysterectomy or permanent sterilization procedure) and urine screen for UTI performed. FMRI procedures again explained to subjects. FMRI performed as described previously in visit 3 for fMRI UUI subjects. Subjects are given instructions and contact numbers to call in the event questions or problems arise. Subjects thanked and subject incentives given or arrangements made to give incentives.



## Flow Diagram 1--- for UII Subjects:

Screening Visit: Study explained to patient. Pt. administered OAB Awareness Tool & given voiding diary instructions. Pt. given copy of consent and either has visit scheduled to sign consent or pt. given research coordinator's info. for future contact

Study Visit #1: Pt returns for study visit with her voiding diary and voiding diary reviewed for study eligibility/UII frequency. Consent Signed. fMRI eligibility assessed. Past medical history & Demographics sheet & baseline questionnaires (OAB-qSF, ISI, PBBC, PISQ-12, IBS Module, CRADI-8, BPIC and vas pain questionnaire administered). POP-Q exam performed if not performed in last 12 months. Cystometrics scheduled. FMRI may be scheduled (for fMRI eligible & willing subjects) @ this visit or arrangements made to contact subjects regarding fMRI. Arrangements made to contact pts for scheduling future appts. and for patients to receive prophylactic antibiotics for catheterization(s). Behavioral Therapy reviewed & handouts given

Study Visit #2: Cystometry explained to subject. Urine pregnancy test and urine screen for UTI performed. Cystometry performed. FMRI patients will undergo fMRI task simulation and have urine and vaginal swab samples collected and stored for possible future analysis. Subjects may undergo hypnotic susceptibility testing at this time or any time prior to initiating study treatment.

Study Visit #3: FMRI (up to 80) Urine screen for UTI and pregnancy test performed. FMRI procedures again explained to subjects. FMRI performed. Subject incentives given or arrangements made to give incentives.

Patients Randomized (N=152). Patients notified of randomization and of pending appointment times and dates  
Pretreatment Expectation question administered

Study Visits #3-10 (or #4-11): 8 **hypnotherapy** sessions over 2 months. CD logs documenting home practice gathered weekly/sent to coordinator. Session(s) taped for quality assurance and randomly audited.

Study Visits #3-10 (or #4-11): 8 **Pharmacotherapy** sessions over 2 months. Medication logs gathered weekly and sent to study coordinator. Session(s) taped for quality assurance and randomly audited.

Study Visit #12: (for pts who had a baseline fMRI & same procedure as Visit #3): F/U fMRI performed and have urine and vaginal swab samples collected and stored for possible future analysis.

Study Visit #12: (for pts who had a baseline fMRI & same procedure as Visit #3) F/U fMRI performed and have urine and vaginal swab samples collected and stored for possible future analysis.

Study Visit #11 (or #13): Final Research Coordinator Meeting with patients after treatment finished (approx. 2-3 months after randomization); f/u questionnaires administered (OABq-SF, ISI, PBBC, PISQ-12, CRADI-8, IBS Module, BPIC questionnaire, Post-treatment Expectation question), voiding diary and treatment compliance information collected. Urine may be collected and stored for possible future analysis. Plans for f/u explained & Contact information re-confirmed. Pt incentives given

6 mo. f/u with patients after treatment finished (approx. 6 months after treatment & may be phone/mail f/u): f/u questionnaires administered (OABq-SF, ISI, PBBC, PISQ-12, CRADI-8, IBS Module, BPIC, Post-treatment Expectation), voiding diary and treatment compliance information collected. Plans for f/u explained & Pt incentives given/mailed. Arrangements made for hypnotherapy patients who choose optional additional hypnotherapy session prior to 12-mo follow-up.

12 mo. f/u with patients after tx finished (approx. 12 months after tx & may be phone f/u): f/u questionnaires administered (OABq-SF, ISI, PBBC, PISQ-12, CRADI-8, IBS Module, BPIC, Post treatment Expectation question), voiding diary and treatment compliance information collected. Pts thanked and Pt incentives given/mailed

## Flow Diagram 2--- for fMRI Normative Controls:

Screening Visit (subject may also sign consent at this visit if desired): fMRI Study explained to subject. Subject administered OAB Awareness Tool and fMRI eligibility assessed. Subject given voiding diary instructions. Subject given copy of consent and either has visit scheduled to sign consent or if subject wishes, may sign consent at this time. If consent has been signed at this visit, the Past Medical History and Demographic forms will be administered at this time. Cystometry and fMRI procedures will be explained to the subject. Appointments for subject to undergo cystometry (see visit 1) & fMRI may be scheduled at this time or subject may be given research coordinator's info. for future contact. Arrangements made for patient to receive prophylactic antibiotics prior to bladder catheterizations.



Study Visit #1 Cystometrics: Subjects (up to 30-35) return for study visit with voiding diary and study eligibility (for fMRI as a normal control) confirmed. Consent signed if this has not happened previously and past medical history/Demographics sheet administered if consent signed at this visit. POP-Q exam performed if not performed in last year. Cystometry explained to subject. Urine pregnancy test and urine screen for UTI performed and have urine and vaginal swab samples collected and stored for future analysis. Cystometry and fMRI task performed. fMRI appointment confirmed.



Study Visit #2 fMRI: Urine screen for UTI and pregnancy test repeated. fMRI procedures again explained to subjects. fMRI performed. Subjects are given instructions and contact numbers to call in the event questions or problems arise. Subjects thanked and subject incentives given or arrangements made to give incentives.

## **4. Selection and Enrollment of Participants**

### **4.1 Inclusion Criteria & 4.2 Exclusion Criteria:**

All study participants must meet all the inclusion criteria as noted below to participate in the study. Additionally, if subjects have any of the exclusion criteria as specified below, they will be excluded from the respective portion of the study.

#### **For the RCT:**

*Inclusion Criteria for the RCT:* Women with Urgency Urinary Incontinence (UUI) who meet inclusion criteria and who choose to participate in the study will be enrolled. They must be able to understand the study procedures and agree to comply with them for the duration of the study. Inclusion criteria:

- Non-pregnant English-speaking women
- > 18 yo
- OAB Awareness scores  $\geq 8$
- $\geq 3$  UUI episodes/week for  $\geq 3$  months

*Exclusion Criteria for the RCT:* Women who have any of the exclusion criteria as specified below will be excluded from study participation

- Women with a history of neurologic diseases such as Multiple Sclerosis, Parkinson's disease, stroke, or dementia
- History of schizophrenia or untreated bipolar disorder or current drug or alcohol dependence
- Women who have taken anticholinergic medications for UUI within the last 3 weeks (women who have taken anti-cholinergics for UUI but discontinued them > than 3 weeks ago may participate in the study) or have a sacral neuromodulator in place to treat UUI or have received Onabotulinum toxin A in the last 12 months to treat UUI
- Contraindications to anticholinergic medications (untreated narrow angle glaucoma, significant urinary retention or gastric retention)
- Pregnant women or lactating women, women who plan to become pregnant in the next year, or pre-menopausal women unwilling to use contraception if engaging in sexual relations during the year of study participation (hysterectomy is considered to be a form of contraception)
- Untreated urinary tract infection
- Prolapse which extends past the hymen (POP-Q points of  $\geq 1+$ ) which may be responsible for UUI symptoms
- Women who cannot keep the majority of the study therapy appointments or those without reliable contact phone numbers or methods of communication with the study personnel.

#### **For the fMRI:**

*Inclusion Criteria for UUI subjects participating in the fMRI portion of the study:* Women with UUI who meet criteria for the RCT and who are willing to participate in the fMRI portion of the study. They must be able to understand the study procedures and agree to comply with them.

*Exclusion Criteria for UUI subjects participating in the fMRI portion of the study:* Women who have any of the exclusion criteria as specified below will be excluded from participation in the fMRI portion of the study

- Women with a history of severe claustrophobia or ferro-magnetic implants such as cochlear implants, cardiac pacemakers or aneurysm clips.

*Inclusion Criteria for normative controls participating in the fMRI study:* These women must be able to understand the study procedures and agree to comply with them. Other criteria:

- Women 46-80 years old\*
- Absence of UUI/OAB symptoms or treatment
- OAB Awareness Tools Scores  $< 8$
- Willingness to undergo fMRI

\*Explanation of age range for the above: In an attempt to assure comparable age ranges of controls to affected UUI subjects, we initially pooled data from both our pilot hypnotherapy and pilot fMRI studies and have found that the median patient age was 54 with the second quartile=46-54, and third quartile=55-62. We initially chose these quartiles as the age range for the normative control group but subsequently found that the age range was overly restrictive in the upper age ranges. We expanded the upper limit to 80 years in order to have flexibility in age adjustment of controls.

*Exclusion Criteria for normative controls participating in the fMRI study:* Women who have any of the exclusion criteria as specified below will be excluded from participation in the fMRI portion of the study

- Women with UUI/OAB
- Women with a history of neurologic diseases such as Multiple Sclerosis, Parkinson's disease, stroke, or dementia
- History of schizophrenia or untreated bipolar disorder or current drug or alcohol dependence
- Pregnant women or lactating women, women who plan to become pregnant in the next year, or pre-menopausal women unwilling to use contraception if engaging in sexual relations during the year of study participation (hysterectomy is considered to be a form of contraception)
- Untreated urinary tract infection
- Women with a history of severe claustrophobia or women with ferro-magnetic implants such as cochlear implants, cardiac pacemakers or aneurysm clips

### **4.3 Study Enrollment Procedures**

#### Identifying and recruiting candidates

Candidates will be identified and recruited based on eligibility criteria. Potential candidates will be identified by UNMH Urogynecology personnel. Subjects will be recruited using a variety of means including phone calls to potential participants and personal contact in clinic. Subjects must be willing and able to give informed consent themselves.

#### Screening log

A screening log of potential participants will be kept with the following information recorded: date of screening, date of informed consent, whether or not subject was enrolled, participant identification number, reason for termination, and whether or not a study termination visit was conducted.

#### Consent procedures

Subjects will be recruited in a private setting (a patient consult or exam room) by a member of the research team. Subjects will be asked if they are interested in study participation in a private setting, and if they verbalize interest, they will be given a copy of the consent forms to read. The patient will be given ample time to consider participation. They will have questions answered by study investigators and be given the opportunity to take the consent home and discuss the study with family and friends or to sign the consent at that time. If they choose to participate after taking the consent home, subjects will be offered arrangements for subjects to return to the study site and sign the consent in the presence of a study investigator, and they will sign the consent in a private setting (consult or exam room or office). Subjects with UUI will be randomized to treatment with either: 1) Pharmacotherapy (a standard therapy for UUI) and conventional behavioral therapy or 2) Hypnotherapy and conventional behavioral therapy. Approximately 152 women will be randomized to hypnotherapy or to pharmacotherapy with approximately half in each group. Up to eighty UUI subjects willing and able to undergo fMRI (who meet inclusion & exclusion criteria) will also participate in the fMRI portion of the study. All subjects will give signed informed consent prior to study treatment. Approximately 30-35 normative control subjects will be recruited and consented in the same fashion as the UUI subjects but will only participate in the fMRI portion of the study as described previously. A total of up to approximately 200 subjects will be enrolled in the study.

## 5. Study Interventions

### 5.1 Interventions, Administration and Duration

UUI subjects will be randomized to hypnotherapy or pharmacotherapy. At their baseline study visit all subjects will receive information regarding standard behavioral therapy (see the “Lifestyle Modification, Behavioral Therapy and Physical Floor Therapy Handout”)

Hypnotherapy: Hypnotherapy will be administered over 8 weeks in 8 sessions by certified, trained clinical hypnotherapists in their outpatient offices. The subjects will be informed that several or all sessions will be audio-recorded and one or more sessions will be reviewed by study personnel to ensure that the hypnotherapist administers the hypnotherapy session in a standardized fashion. Recordings will be stored on the research computer and access to these recordings will be available to assigned research personnel only. All recordings will be stored for approximately 7 years, in the same fashion as other data, and then will be destroyed. The hypnotherapists have been instructed to not use the patients’ name or any other identifiers during the recorded session. Sessions will last approximately 1 hour with a brief outline of these sessions as follows; Session #1: The hypnotherapist will explain hypnotherapeutic principles; subjects will inform the hypnotherapist regarding any phobias or fears (so that these triggers will be avoided). Subjects will undergo their 1<sup>st</sup> hypnotherapy session and hypnosis will then be terminated. Session #2: address emotions around OAB and life impact, visualize pelvic floor exercise mechanics, and undergo their 2<sup>nd</sup> hypnotherapy session followed by termination of hypnosis. Subjects may choose to either receive a CD or to download a digital recording (for use on a digital device) specially prepared for them to for home practice of hypnotherapy sessions. This will occur at either their 2<sup>nd</sup> or 3<sup>rd</sup> hypnotherapy session; they will be instructed NOT to listen to the hypnotherapy CD/digital recording while driving and encouraged to listen to the CD/digital recording daily and record the home use of their CD/digital recording. Session #3,4,5,6,7; same as session 3. Session #8: same as previous sessions. In addition, the subjects will be counseled to expect occasional and temporary setbacks in their bladder symptoms and the hypnotherapist and subject will discuss how to cope with these setbacks. The details of these sessions are detailed in the “Hypnotherapy Session Guidelines” (see Attached MOP). Following the 8 weeks of therapy, subjects will be encouraged to continue to practice self-hypnosis and/or listen to their home practice CD/digital recording given to them and this practice will be tracked for the 1 year duration of the study. Hypnotherapy patients will also have the opportunity to have one additional hypnotherapy session prior to their 12-month follow-up visit: arrangements for the session can be initiated at their 6-month follow-up visit.

Potential adverse effects of hypnotherapy include: a) “False Memory Syndrome”: Although, in the 1980s ‘false memory syndrome’ was described with the use of hypnotherapy in child abuse survivors, the current practice of hypnotherapy uses a much different approach to this therapeutic application. Current practice includes open-ended lines of questioning as opposed to suggestive or leading lines of questioning utilized in the 1980s with these victims. Transformation of hypnotherapy practices has greatly decreased occurrence of false memory syndrome, indeed calling into question its true existence. Recently, the hypermnesia attributed to the hypnotic state has been rejected based on more rigorous research.<sup>22</sup> Last, the use of hypnotherapy in this study is for UUI treatment and recall of emotionally traumatic events will not be part of the protocol. Thus, serious risk to subjects undergoing hypnotherapy for UUI is negligible. b) Possibility that hypnotherapy is ineffective adjunctive treatment for urgency urinary incontinence & potential risks regarding home practice hypnotherapy CD/digital recording: Hypnotherapy subjects will be clearly instructed to use their home practice CD/digital recording only when and where they are can pay full attention to the CD/digital recording. Specifically they will be instructed NOT to drive and listen to the hypnotherapy home practice CD/digital recording. It is possible that hypnotherapy is ineffective in urgency urinary incontinence treatment. In this case, the subjects will have been inconvenienced because of the time devoted to the hypnotherapy sessions.

Pharmacotherapy: Pharmacotherapy counseling sessions will be administered over 8 weeks in 8 sessions by trained personnel in private settings either at UNMH or UNM CTSC outpatient clinic rooms or administrative offices. The subjects will be informed that several or all sessions will be audio-recorded and one or more sessions will be reviewed by study personnel to ensure that the medication counselor administers the hypnotherapy session in a standardized fashion. Recordings will be stored on the research computer and access to these recordings will be available to assigned research personnel only. All recordings will be stored for approximately 7 years, in the same fashion as other data, and then will be destroyed. The medication counselors have been

instructed to not use the patients' name or any other identifiers during the recorded session. Subjects will be scheduled for in person visits with the medication counselor who will review medications and their side effects. However, if subjects state these in person visits are overly burdensome, these visits may occur via phone as long as the patient comes in for at least 2 of the subsequent visits for pill dispensation which should occur midway and at the end of the 8 sessions. These sessions will take as long as required/desired for subjects to feel that they have received adequate instruction/counseling. Discussion of strategies to cope with their bladder symptoms will occur. The expected side effects of medications (such as dry mouth, constipation) will be discussed and strategies to cope with side effects will also occur. It is expected that these sessions will take approximately 20-60 minutes, depending on the subjects' needs. The medication may be modified if the patient complains of side-effects from the initial anti-cholinergic or perceives that her response in UUI treatment is inadequate; a different anti-cholinergic may be given to the patient if she requests a different UUI medication. The study will use either of two standard, long acting anti-cholinergic medications and dosages (Long acting Tolterodine 4mg/day or Extended Release Oxybutynin 10 mg/day or their equivalent generic substitutes). Initial medication use will usually be Oxybutynin 10 mg/day but will depend on the patient history (for example those who have used Oxybutynin unsuccessfully will be given Tolterodine and vice versa). A recent AHRQ meta-analysis found that there was no difference in effectiveness or side-effects between the available anti-cholinergics used to treat UUI as long as the medications were extended release formulations, such as those used in this study.<sup>38</sup> The details of these sessions are in the "Pharmacotherapy Session Guidelines" (see Attached MOP). Following the 8 weeks of therapy as described previously, subjects will continue to take their anti-cholinergic medications and continued use of medication will be tracked for the 1 year duration of the study.

Potential adverse effects of pharmacotherapy: Subjects randomized to pharmacotherapy will be instructed take a standard anticholinergic extended release dose (see above) for urgency incontinence. Subjects with major contraindications to anticholinergic medications will be excluded from study participation (see exclusion criteria). Serious adverse events related to anticholinergic medications are rare, however mild side-effects are relatively common; these include dry mouth, constipation, dyspepsia or mild nausea, dry eyes, and change in urination such as urinary hesitancy.<sup>38,54</sup> Subjects in this proposal will be informed regarding potential side effects of medications, will keep medication logs and will regularly meet with a medication counselor to review these side effects. Minor side effects may include symptoms such as dry mouth, dry eyes or constipation. The original anti-cholinergic may be changed to a different long acting anti-cholinergic for UUI if the patient finds the minor side effects to be bothersome and wishes to change medications. Serious medication related adverse events occur the medication will be discontinued (see protection against risks below). If subjects report urinary retention or other symptoms of concern to the medication counselor, subjects will be instructed to stop the medication. Simultaneously a clinic visit to the UNM Urogynecology Clinic will be arranged so that subjects may be appropriately evaluated. These measures will decrease the risk of harm from study participation.

Functional MRI: The UUI subjects (approximately half from the hypnotherapy group and half from the pharmacotherapy group) willing to have an fMRI and without contraindications to fMRI will participate in the fMRI portion of the study and will undergo a baseline fMRI and a follow-up fMRI at the conclusion of their 8 weeks of treatment (as described above). Approximately 30-35 normative controls will also undergo one fMRI. All subjects will have urine dipstick testing and pregnancy testing (in women who are premenopausal and without a history of a hysterectomy or permanent sterilization) performed prior to fMRI: subjects who are pregnant or who have a urinary tract infection may not undergo fMRI testing. The fMRI protocol is below. In brief, FMRI subjects will have a bladder catheter placed and will be asked to a) concentrate on a picture placed before them while they have the MRI performed b) they will next have their bladders filled with sterile fluid and be asked to rate the degree of bladder discomfort or "urge to void" experienced during bladder filling c) they will then have the catheters removed, the amount of urine voided will be measured and subjects will be discharged to home and given instructions to contact the study personnel if questions or problems arise. The time required for each fMRI session is approximately 1-2 hours.

## FMRI PROTOCOL:

### FMRI Data Acquisition:

High resolution T1 [TE (echo time) = 1.64 ms, TR (repetition time) = 2.53 s, 7° flip angle, number of excitations (NEX) = 1, slice thickness = 1 mm, FOV (field of view) = 256 mm, resolution = 256 x 256] anatomic images will be collected on a 3 Tesla Siemens Trio scanner at the beginning of each experiment. For each of the FMRI tasks, echo-planar images will be collected using a single-shot, gradient-echo Introduction: The fMRI portion of this study will be performed at the Mind Research Network (MRN). The study investigator at the MRN has extensive experience evaluating the role of the ACC and anterior insula in error monitoring, cognitive control and the perception of pain. His team has investigated the role of the ACC and anterior insula in the subjective experience of pain. Specifically, participants were requested to continuously rate their subjective experience of pain on a Likert scale from 0-10, with the scale being updated at a 10 Hz frequency. Functional results indicated that this subjective regressor captured unique variance related to the experience of pain in the ACC and anterior insula compared to traditional modeling techniques.

### FMRI Subject and Task:

Study participants will complete two tasks while undergoing FMRI. Presentation software will be programmed to control stimulus presentation, synchronize stimulus events with the scanner and collect response data for offline analyses. A non-ferrous key-press device will be positioned directly under the subject's right hand to continuously (10 Hz sampling frequency) record current voiding urge levels on an 11-point Likert scale (0 = "no urge" to 10 = "worst urge imaginable"). To minimize neuronal activation associated with eye movements, subjects will be instructed to maintain visual fixation throughout all trials on the centrally presented cross. An eye-tracking device will be used to record saccades during the experiment.

**Task A:** For this task, participants will be asked to continuously rate their urge levels to void while maintaining centrally presented cross. During this time, participants' bladders will be filled following the methods described by Griffiths et al.<sup>35</sup> A urethral catheter will be placed into the bladder for bladder filling/emptying. A small volume of saline solution (usually 50-100 ml depending on individual subject's urge sensations noted on cystometry) will be introduced into the empty bladder following which the solution will be repeatedly infused into and withdrawn from the bladder while functional brain imaging is performed. The infusion/withdrawal cycle will be performed, more liquid being infused than withdrawn. The bladder will then be filled further until the subject signals strong bladder sensation. The volume at which this sensation occurs will be recorded and beginning at this bladder volume infusion/withdrawal cycles will be repeated during fMRI scanning. Two to 4 blocks will be performed, depending on the level of subject discomfort.

**Task B:** All participants will be asked to maintain fixation on a centrally presented cross. This data will be used in conjunction with the results from Task A to perform functional connectivity analyses. All participants will complete two FMRI runs of this task totaling 10 minutes of acquisition time. Both of these tasks will initially be performed by control subjects without symptoms of OAB as confirmed by the OAB-q questionnaire. Control subjects will be imaged to provide normative values for ACC, AI and OFC activation in our imaging facility and confirm that we are able to replicate the differences between control and UI subjects demonstrated in prior work. The same tasks will be performed twice on UI subjects entering the study. Subjects with UI will undergo fMRI scanning during performance of both tasks before therapy and following therapy. Volumes of saline solution instilled in the second phase of Task A during the pre-therapy fMRI will be recorded. Identical volumes will be instilled during the post therapy scanning of subjects with UI. For the fMRI tasks, echo-planar images will be collected using single-shot, gradient-echo planar pulse sequences. The first image of each run will be eliminated to account for T1 equilibrium effects in addition to the two dummy scans that are part of the Siemens sequence.

**FMRI Image Processing:** The methods used to analyze FMRI data will be similar to those employed by our team in previous studies. Specifically, the current analyses will closely parallel a recent experiment that was conducted by the research team in which subjective ratings of pain were recorded. In that study data were generated in a task which required participants to subjectively rate their pain to a cold pressor stimulus. We modeled the regressors corresponding to the application of the stimulus (cold temps) as well as the individual subject's pain ratings separately. Preprocessing steps of fMRI data obtained during both tasks will include slice correction, temporal auto-correlations correction and motion correction. For task A, a voxel-wise multiple regression analysis will be used to estimate the beta weights corresponding to the functional activation resulting from each of the separate conditions. The multiple regression will contain one individually tailored demeaned regressor corresponding to each individual subject's urge to void (urge regressor). The urge regressor will resemble a step function, with each button press signaling the onset of either increasing or decreasing subjective levels of urge to void. The resulting step functions will then be convolved with a gamma variate function derived from known

parameters of the hemodynamic response. In addition, a regressor corresponding to the inflation and the deflation of the bladder will be created by convolving the experimental time-course with a gamma variate function

Potential adverse effects of fMRI and bladder catheterization: a) fMRI: These risks are small as MRIs are commonly performed clinical procedures without significant risk and without radiation exposure. Subjects will be screened to rule out the presence of metallic objects prior to the MRI scan as an MRI machine is essentially a large magnet capable of moving iron containing objects. Absolute caution will be implemented to ensure that only non-ferrous objects are present during all of the MRI sessions. Participants will be asked to change into hospital scrubs prior to being placed in the scanner to ensure that they do not introduce any metallic objects into the imaging environment. Participants will also be screened for the presence of a pacemaker or any other metallic objects in their body, such as an aneurysm clip, ear implant, or nerve stimulator. Participants with these or other metallic devices will not be allowed to participate in the study. As the effects of MR on pregnancy have not been fully studied, subjects are pregnant will be excluded from the study. The MRI may also cause claustrophobia and anxiety from loud noises made by the machine. A two-way intercom system and a video monitoring system will provide continual monitoring of the subject's condition. If discomfort or concern is expressed or detected, the experiment will be stopped and the subject will be given the option to discontinue at any time. Ambient scanner noise will be below current recommended guidelines.

b) Bladder catheterization: In addition to bladder catheter placement for cystometric evaluation those subjects who participate in the fMRI portion of the study will also be catheterized at the time of fMRI in order to fill the bladder (see fMRI above). The risks of bladder catheterization, although unlikely, include dysuria, hematuria and urinary tract infection. A meta-analysis concluded that prophylactic antibiotics for complex bladder testing decreased significant bacteriuria with few side-effects, with a reported range of bacteriuria of 1-8% in the groups treated with antibiotic prophylaxis.<sup>46</sup> To decrease infection risks of bladder catheterization during this study, prophylactic antibiotics will be given to all subjects prior to and for the day of catheterization. Nitrofurantoin or Trimethoprim/Sulfamethoxazole will be administered prior to and for the day of catheterization. Subjects allergic to these medications will be given appropriate alternate antibiotic prophylaxis. Prior to the procedure, the patient will be informed regarding the procedure protocol and potential discomforts and side-effects. Participants will be clearly informed of their right to withdraw from the study at any time. Catheterization will be performed using sterile technique by nursing staff whose standard practice is to perform this procedure. Additionally, subjects will have urine dipsticks checked at study entry and prior to bladder catheterization to ensure absence of urinary tract infections. Subjects noting persistent urinary tract infection symptoms following the tasks will have urine dipstick testing and a urine culture performed. Subjects with evidence of a urinary tract infection will be treated and urinary infection occurrence will be tracked.

## **5.2 Handling of Study Interventions**

This study involves the use of long-acting Oxybutynin (Ditropan XR 10 mg) and long acting Tolterodine (Detrol LA 4 mg), or their equivalent generic substitutions, as pharmacologic therapy for urgency urinary incontinence. These medications will be ordered in bulk by the research pharmacist and stored with the research pharmacy. The medications will be signed out from the research pharmacist to the research coordinator for the study participant. The Investigators will request that subjects to return unused medications to the research coordinator who will in turn return the unused medications to the pharmacy. A research pharmacy accounting log tracks medications issued to subjects and records information including date, dose number, amount received, patient ID, initials of recorder, and initials of person dispensing drug as well as medications returned. Please refer to the MOP Chapter—Pharmacotherapy Handling Chapter and Accountability Log.

For behavioral interventions, pharmacotherapy counseling and hypnotherapy interventions, please refer to previous section 5.1. None of these interventions will be masked.



## 5.3 Concomitant Interventions

### 5.3.1 Allowed Interventions

- Behavioral Interventions and Pelvic Floor Exercise (see 5.1)
- IF subjects are already engaging in the following activities, they will be allowed. Subjects will be requested to inform the study coordinator if they initiate these activities during the 12 months that they participate in the study.
  - Meditation
  - Yoga
  - Acupuncture for non-UUI indications
  - Tai Chi

### 5.3.2 Required Interventions

- Hypnotherapy (if randomized to hypnotherapy group)
- Medication Counseling and Ditropan XR or Detrol LA or their generic substitutions (if randomized to pharmacotherapy group)

### 5.3.3 Prohibited Interventions

- No other anticholinergic medications (such as Toviaz®/Fesoterodine or Sanctura®/Trospium or Vesicare®/Solifenacin or Enablex®/Darifenacin) or beta 3 agonists (such as Myrbetriq®/Mirabegron) for UUI should be taken by research subjects for the year they participate in the study
- Sacral Neuromodulation for UUI treatment (neuromodulators programmed for other indications are allowed)
- Onabotulinum toxin (“Botox”) injected intravesically for UUI treatment in the last 12 months
- Acupuncture specifically administered to treat UUI
- Herbal remedies specifically designed to treat UUI

## 5.4 Adherence Assessment

Non-adherence/Non-Compliance to treatment or use of off-protocol therapies will be defined as follows—

### Non-adherence/Non-Compliance to treatment protocol at 2 month follow-up of the study:

*Definition Non-adherence/Non-Compliance:*

- Medication group: Subjects state ‘no’ on the Pharmacotherapy Compliance form (question #1) that they are no longer taking their medications at 2 month follow-up
- Hypnotherapy group: Attendance of < 60% of hypnotherapy appointments

*Measures of adherence and compliance and steps taken to improve non-adherence during 1<sup>st</sup> 12 weeks of the study:* Data on adherence to the treatment protocol will be collected weekly during the treatment phase of the study by research staff and reviewed monthly by the PI. Pharmacotherapy adherence/compliance will be tracked with the compliance questionnaires at 2, 6 and 12 months. Hypnotherapy adherence/compliance will be tracked by hypnotherapy session compliance and with compliance questionnaires at 2, 6, and 12 months. Off-protocol treatments used will also be tracked based on the compliance questionnaires administered at 2, 6 and 12 months. Data on adherence will be reviewed at each of the DSMB meetings (described subsequently). Available data on the use of anti-cholinergics for urgency urinary incontinence suggests an overall non-compliance or withdrawal rate of 30% in randomized controlled trials.<sup>54</sup> In clinical practice discontinuation rates have been reported to be even higher with continuation rates less 45% at 1 month and 13% at 1 year.<sup>21</sup> If average adherence falls below the suggested rate of 60%, a conference call will occur for study investigators to discuss methods for improving adherence without affecting the integrity of the study. However, given the data regarding anti-cholinergic side effects, it is quite possible that this non-adherence rate is not changeable. Protocol adherence in subjects randomized to hypnotherapy will be measured by monitoring compliance in keeping hypnotherapy

appointments. If adherence of hypnotherapy subjects falls below a suggested rate of less than 60%, a conference call for study personnel to discuss methods for improving treatment adherence will occur.

*Non-adherence/Non-Compliance or use of off-protocol therapies at 6, 12 month follow-up visits*

*Definition of Non-adherence/Non-Compliance at 6 & 12 month follow-up:*

- Medication group: Subjects state 'no' on the Pharmacotherapy Compliance form (question #1) that they are no longer taking their medications at 6 or 12 month follow-up
- Hypnotherapy group: Subjects who state 'no' on the Hypnotherapy Compliance form (question #1) that they are not listening to their hypnotherapy CD/digital recording or practicing self-hypnosis at 6 or 12 month follow-up

*Definition of use of off-protocol treatments*

- Subjects use other treatments for UUI such as sacral neuromodulation, intravesical botox in the last 12 months or other UUI medications (such as Toviaz®/Fesoterodine or Sanctura®/Trospium or Vesicare®/Solifenacin or Enablex®/Darifenacin or Myrbetriq®/Mirabegron)
- Subjects use acupuncture to specifically to treat UUI
- Subjects use herbal remedies specifically to treat UUI

*For Analysis of non-compliance or use of off-protocol treatments:* See Section 9.5. Subjects who are non-compliant or use off-protocol therapies will still be analyzed in their assigned treatment groups in the ITT analysis. When subjects implement off-protocol therapies, we will examine the sensitivity of the per protocol analyses in two ways. First, we will modify the models to incorporate a time-varying treatment parameter that can be used to examine the effect of received treatment. Second, we will censor all measurements after they receive alternative treatment, and then impute all censored measurements based on information collected from those who do not switch. Non-Compliance will be analyzed in the per-protocol analysis first as a categorical variable (yes/no) in its relationship to the outcome(s) and will then be evaluated as continuous variables (i.e. number of times self-hypnosis practiced or CD/digital recording used) and its relationship to the outcome(s).

## 6. Study Procedures: 6.1 Schedule of Evaluations—Table 1.

Assessment & Evaluation Tools	Screening Visit Day	Enroll V 1 Day -60 --1	Cystom. V2 Day -60- -1	fMRI V3 Day -60--1	Randomize Treatment Day 0	Treat1 V3orV4 Week 1	Treat2 V4orV5 Week2	Treat3 V5orV6 Week 3
Inclusion/ Exclusion	x	x						
Informed Consent		x						
Eligibility Form/ OAB Awareness Tool	x	x						
Eligibility Form fMRI	x	x		x				
Demographic & Medical Hx Forms & POP-Q (if without in last yr)		x						
Voiding Diary		x						
OABq-SF,ISI, PPBC, PISQ-12,CRADI-8, IBS module, BPIC +VAS		x						
Expectation Question-baseline					x			
Expectation Question-Follow-up								
Stanford Susceptibility Test (choices of times=x)		x	x	x				
Pregnancy Test			x	x				
Urine Dipstick			x	x				
Cystometry procedure Checklist & Cystometry Data Form			x					
fMRI procedure Checklist				x				
fMRI Task sheet and urine and vaginal swab sample collected and stored for possible future analysis.			x	x				
Incontinence Log & Med or Hypnotx CD logs						x	x	x
Adverse Events			x	x		x	x	x

Assessment & Evaluation Tools	Treat4 V6orV7 Week 4	Treat5 V7orV8 Week 5	Treat6 V8orV9 Week 6	Treat7 V9or V10 Week 7	Treat8 V10or V11 Week 8	fMRI V12 Week 9	Followup End Tx V11or13 Week 8-10	Followup 6 mo Mo 6	Followup 12 mo Mo 12
Voiding Diary							x	x	x
OABq-SF, ISI, PPBC, PISQ-12, IBS module, CRADI-8, BPIC							x	x	x
Expectation Question-baseline									
Expectation Question-Follow-up							x	x	x
Urine and vaginal swab sample collected and stored for possible future analysis							x		
Incontinence Log & Med or Hypnotx CD logs	x	x	x	x	x				
Medication or Hypnotx Compliance Questionnaire							x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x
Pregnancy Test						x			
Urine Dipstick						x			
fMRI procedure Checklist						x			
fMRI Task sheet filled and urine and vaginal swab sample collected and stored for possible future analysis.						x			

## **6.2 Description of Evaluations**

### **6.2.1 Screening Evaluation**

**Screening visit** – Potential participants will be screened by the coordinator/Study personnel before enrollment to determine eligibility for the RCT portion of the study based on inclusion/exclusion criteria. Subjects will also be screened for fMRI eligibility; *however* if the subject is ineligible for the fMRI, they may still participate in the RCT portion of the study. In general, the consent will be obtained within 4-6 weeks of the screening visit but subjects will be given all the time necessary to decide whether or not they want to participate in the study.

Subjects in the UNMH Urogynecology clinics with UI who qualify for study entry will be asked whether they are interested in study participation. These subjects will be assured that declining study participation will not affect their clinical care. In addition, women with UI who contact the UNMH Ob-Gyn research division expressing interest in study participation will have the study explained to them and follow the same procedures as UNMH subjects (see following). Potential subjects will be given a copy of the study consent for their review. Those who are interested will be administered the OAB Awareness tool, a validated measure which screens for presence of OAB, to screen whether or not they are candidates for the study. They will also be instructed how to keep a voiding diary, if this has not already been done, as it is the standard of clinical care for all subjects with UI. If they ultimately choose to participate in the study, they will be asked to bring the diary with them for Visit 1 (below). The patient will be given the option to schedule Study Visit 1 or given the option to contact the study coordinator to schedule Study Visit 1 at a later date if they are uncertain regarding study participation.

### **6.2.2 Enrollment, Baseline Visit/Evaluation and Randomization**

#### **Enrollment/Consent & Baseline Visit for women in RCT (Day -60 to -1):**

Informed Consent Process: Written informed consent will be obtained from each subject at study entry. And will be obtained by the following process:

- 1) Subjects will be asked if they are interested in study participation in a private setting, and if they verbalize interest, a copy of the consent forms will be explained and given to them to review so that they may discuss the study with family and friends.
- 2) The PI or Co-Is will meet with subjects to review the consent form and confirm the subject's understanding of the study and to answer their questions. Subjects will answer screening questions to ensure they are appropriate candidates for the study.
- 3) If subjects state that they are interested in study participation after explanation of the study as noted previously, an appointment will be made for subjects to return to sign the consent and fill out the baseline information and questionnaires.
- 4) If they state that they are not certain, they will be given the study coordinator's contact information so that they can call study personnel if they decide to participate in the study; a study appointment will be made for subjects to return to sign the consent after they contact study personnel.
- 5) At the enrollment appointment, which occurs in a private setting, subjects sign the consent after study personnel are certain that subjects have had appropriate counseling and understanding regarding the study and that the study and consent have been explained to them in a fashion congruent with their medical literacy. Consent will be obtained after screening is performed and will be re-reviewed in the future in the event changes are required. In general, consent will be obtained at the baseline visit. The PI or Co-Is, Study Coordinator(s) or Study Nurse(s) will obtain verbal and written informed consent on one IRB approved consent after explaining study and before collecting any data. Human subject's protection will follow local and national regulations at all times.

Baseline assessments include:

- Questionnaires – OABq-SF, ISI, PPBC, PISQ-12, CRADI-8, IBS Module, IC & VAS pain questionnaire
- Voiding Diary
- Demographics form
- Medical history form
- POP-Q examination if one has not been performed during their routine clinical examination

within the last year (Pelvic Organ Prolapse Quantitation Exam, a validated examination recommended by the International Continence Society to standardize quantitation of patients' prolapse)

Arrangements will be made for cystometric testing, Stanford hypnotic susceptibility testing, and fMRI testing (if the subject is willing and without contraindications to fMRI). The expectation question will also be explained to subjects but will not be formally administered until the subject has been randomized to treatment. Adverse events will be tracked and followed up appropriately as noted in the DSMP. Subjects willing to participate in the fMRI study will be screened regarding whether or not they meet criteria for entry into the fMRI study. Subjects who meet criteria and who are willing to participate in the fMRI portion of the study will be scheduled for their fMRI or arrangements will be made to contact the subject to inform them of the date/time of their fMRI. The subjects will be randomized within a month of obtaining the consent.

**Enrollment/Consent & Baseline Visit for *Normative Controls ONLY* participating in fMRI study (Day 0):** In addition to the UUI study subjects described previously, a group of women without UUI and without OAB symptoms (also determined by the OAB Awareness Tool screening questionnaire) will be enrolled. This normative group (approximately 30-35 subjects) will keep voiding diaries, answer questionnaires, and undergo urine pregnancy and dipstick testing and cystometric testing followed by performance of an fMRI in order to compare baseline fMRIs in women with and without UUI. The consenting process will be the same as described for the UUI subjects. For this group of women, cystometrics may be performed the same day they are enrolled and fMRI will be scheduled for the following week (if this is not possible, the fMRI should be scheduled within 2 weeks). The procedures will be performed as outlined previously and subsequently in 6.4.3 and 6.4.4.

### **Baseline Cystometrics**

**Cystometrics (Day -60 to -1)** Cystometric testing (a bladder filling test during which patient sensations are recorded at various volumes and evidence of stress or urgency incontinence recorded) will be performed. Testing includes a urine pregnancy test and urine dipstick. See MOP Chapter "Study Procedures" regarding forms to be filled. If subject chooses to undergo an fMRI, they will have simulation of their fMRI task performed and may have urine and vaginal swab samples collected and stored for possible future analysis (For example, urine may be analyzed for biomarkers and microbiome analysis. See MOP Chapter "Study Procedures" regarding forms to be filled as noted in Section 5.1.

### **Baseline FMRI**

**FMRI (Day -60 to -1 for baseline and week 9 for follow-up)** will be performed on women willing and able to have fMRI at baseline and follow-up. Testing includes a urine pregnancy test and urine dipstick. Forms to be completed include the fMRI procedure are noted in the "Study Procedures" MOP and has been described in the Protocol Section 5.1.

### **Other Baseline Tests/Questionnaires**

**Stanford Hypnotic Susceptibility Testing (Day -60 to week 1)** this validated test may be administered by the hypnotherapist any time before the subject receives either their pharmacotherapy or hypnotherapy intervention. Its administration depends primarily on scheduling issues between the subject and hypnotherapist; attempts will be made to couple this testing with any of the subjects' pre-treatment visits (enrollment, cystometrics, fMRI) though the subject may have to come for a separate visit if this is not possible.

**Patient Expectation Question (Day 0 and prior to treatment)** the subject will be administered this question after randomization and prior to treatment. The question will be explained to the patient at enrollment, but will not be administered until the patient is notified regarding her group assignment by the Research Coordinator or her designee.

## Randomization

**Randomization to Treatment (Day 0)** Subjects will be informed of their randomization to treatment by the Research Coordinator (or her designee if she is absent). Please refer to Statistics Section 9. Randomization will occur within 2-months of Enrollment. Treatment visits will be initiated within one month following randomization with a goal of initiating treatment within 1 week. However, subjects will be given the necessary time to prepare for their upcoming weekly treatment sessions.

### 6.2.3 Blinding

This study is a single blinded trial. Every effort will be made to maintain masking until the study's completion of treatment of the 152 subjects in the RCT. Investigators involved in analyzing fMRIs, Co-Is, other than Dr. Sapien, participating in the RCT, study personnel performing data entry and the study statistician will be blinded to knowledge of subjects' treatment groups. Investigator blinding will only be breached if a subject suffers an unexpected clinical event and investigator knowledge of the subject's treatment is essential to providing standard of care. Subjects cannot be blinded to treatment interventions as it will be obvious to them whether or not they are undergoing hypnotherapy or taking medications.

### 6.2.4 Treatment Visits

**Treatment Visits (weeks 1-8)** Depending on randomization, participants will either undergo medication counseling sessions or hypnotherapy sessions. These visits are expected to be initiated within one month following randomization with the goal of initiating treatment within 1 week of randomization. However, subjects will be given the necessary time to prepare for their upcoming weekly treatment sessions. These visits are expected to be completed within 8 weeks of initiation of the first treatment.

The number of sessions attended by subjects will be recorded. The Medication side effects/incontinence log and the Hypnotherapy CD-digital recording use/incontinence logs will be collected at the visits. Please refer to section 5 for details.

### 6.2.5 Follow-up Assessments

All subjects will have follow-up assessments irrespective whether they discontinue study interventions or are non-compliant with interventions or use off-protocol treatments.

**Follow-up Assessment at End of Treatment (weeks 8-10 depending on whether subject had fMRI):** A subject visit will be arranged by study personnel for the post-treatment (end of counseling/hypnotherapy session) assessments which should occur within 2 weeks of finishing the treatment sessions for those subjects not undergoing fMRI or within 3 weeks of finishing treatment for those who will also undergo a follow-up fMRI. Subjects may have urine and vaginal swab samples collected and stored for possible future analysis (For example, urine may be analyzed for biomarkers).

The assessments and visit will include

- Questionnaires; OABq-SF, ISI, PPBC, PISQ-12, CRADI-8, IBS Module, and IC questionnaire. Follow-up Expectation Question and Compliance Questionnaire
- Voiding Diary
- Subject feedback regarding study participation
- Confirm subject contact information (patient email address, mailing address, cell and landline phone numbers, name/address/phone number of friend or relative in event of difficulty contacting patient)
- Confirm arrangements for patient incentive payments and for follow-up in 6 months

**6 month Follow-up (month 6)** the Study Coordinator or her designee will arrange 6 month follow-up assessment visits for subjects. Although it is preferable to have an in-person visit, it is possible to have the visit performed via phone and mail. Patient reimbursements will be paid at the in-person visit. If the subject has a phone/mail visit arrangements for reimbursement will be made following completion of this visit. The follow-up assessment should be completed within 5-7 months of completion of hypnotherapy or pharmacotherapy sessions.

Final assessments & follow-up include

- Questionnaires; OABq-SF, ISI, PPBC, PISQ-12, CRADI-8, IBS Module and IC questionnaire. Follow-up Expectation Question and Compliance Questionnaire
- Voiding Diary
- Subject feedback regarding study participation
- Confirm subject contact information (patient email address, mailing address, cell and landline phone numbers, name/address/phone number of friend or relative in event of difficulty contacting patient)
- Confirm arrangements for patient reimbursement and for follow-up at 12 months

### 6.2.6 Completion/Final Evaluation

**12 month Follow-up (month 12)** The Study Coordinator or her designee will arrange 12 month follow-up assessment visits for subjects. Although it is preferable to have an in-person visit, it is possible to have the visit performed via phone and mail. Patient reimbursements will be paid at the in-person visit. If the subject has a phone/mail visit arrangements for reimbursement will be made following completion of this visit. The follow-up assessment should be completed within 10-14 months of completion of hypnotherapy or pharmacotherapy sessions. These same evaluations will be needed for subjects who discontinue study interventions early. Potential reasons for early termination include events which results in distress to the subjects as a result of study participation (See Chapter 7 Safety and Chapter 8 Intervention Discontinuation) and follow-up for all subjects who discontinue interventions but are willing to continue to participate in the study will be the same as though who continue the interventions (12 months).

Final assessments & follow-up include

- Questionnaires; OABq-SF, ISI, PPBC, PISQ-12, CRADI-8, IBS Module and IC questionnaire. Follow-up Expectation Question and Compliance Questionnaire
- Voiding Diary
- Subject feedback regarding study participation
- Thank subjects for study participation

## 7. Safety Assessments

Potential complications of the study interventions will be tracked (as described subsequently) and include the following;

### Hypnotherapy

- *Severe emotional upset*
- *CD/digital recording use while performing activities requiring intense concentration (driving)*

*'False Memory Syndrome' and severe emotional upset---* *Relevant background, management and modification of intervention or participant assessments:* Although, in the 1980s 'false memory syndrome' was described with the use of hypnotherapy in child abuse survivors, the current practice of hypnotherapy uses a much different approach to this therapeutic application. Current practice includes open-ended lines of questioning as opposed to suggestive or leading lines of questioning utilized in the 1980s with these victims. Transformation of hypnotherapy practices has greatly decreased occurrence of false memory syndrome. Recently, the hypermnesia attributed to the hypnotic state has been rejected based on more rigorous research.<sup>22</sup> Last, the use of hypnotherapy in this study is for UUI treatment and recall of emotionally traumatic events will not be part of the hypnotherapy protocol. Thus, serious risk to subjects undergoing hypnotherapy for UUI is negligible. If a subject reports severe emotional upset attributed to the sessions, her sessions will be terminated. In the unlikely event that >33% of study subjects report that they experience serious emotional upset from study participation the study will be suspended and a review will occur. If these events are found to be attributable to hypnotherapy, the study will continue to be suspended until the hypnotherapy protocol is re-evaluated and revised (see below). Serious emotional upset includes inability to work or events that would necessitate evaluation by a physician or care provider. It is highly unlikely that hypnotherapy would unmask or de-repress significant emotional upset (e.g. hysteria, uncontrollable anger or hostility) in subjects. The potential for this occurring will be minimized by excluding subjects with a history of schizophrenia or untreated bipolar disorder and by having the hypnotherapist guide the sessions and terminate sessions if subjects are beginning to show signs of undue duress during hypnotherapy. Although other hypnotherapy studies have not reported significant



emotional upset as a complication, we believe that it is prudent to prepare for this unlikely possibility. A report of a subject experiencing serious emotional upset from study participation will result in a meeting of the PIs and review of the issues surrounding its occurrence. The PIs and Study Coordinator will generate a report, assess whether it was preventable, and develop an action plan to prevent recurrence including protocol revision and this report will be given the DSMB. While this occurrence is very unlikely, we recognize that sporadic occurrence of emotional upset is possible in any setting. In the very unlikely event that a third of subjects complain of significant emotional upset, the study should be halted until the circumstances surrounding its occurrence are investigated in depth.

*Use of CD/digital recording while performing activities requiring intense concentration (driving)--Management and modification of intervention or participant assessments:* Hypnotherapy subjects will be clearly instructed to ONLY use their hypnotherapy home practice CD/digital recording when and where they are can pay full attention to the recording. They will clearly be instructed NOT to listen to the hypnotherapy CD/digital recording during activities which require their full attention; specifically the will be instructed NOT to drive and listen to the home hypnotherapy practice CD/digital recording. If it is found that subjects listen to the CD/digital recording while they are driving, the PIs and Study Coordinator will generate a report and develop an action plan including protocol revision which will be given to the DSMB.

#### Pharmacotherapy:

- *Constipation*
- *Dry Eyes*
- *Dry mouth*
- *Dyspepsia or Nausea*
- *Urinary Hesitancy or Retention*

*Relevant background, management and modification of intervention or participant assessment for the above:* Serious adverse events related to anticholinergic medications are rare, however mild side-effects are relatively common; these include dry mouth, constipation, dyspepsia or mild nausea, dry eyes, and change in urination such as urinary hesitancy, as reported in an AHRQ and Cochrane meta-analysis.<sup>38,54</sup> Subjects in this proposal will be informed regarding potential side effects of medications, will keep medication logs and will regularly meet with a medication counselor to review these side effects. If symptoms such as dry mouth, dry eyes, dyspepsia or constipation occur, if the patient finds the minor side effects to be bothersome and wishes to change medications the original anti-cholinergic may be changed to the alternate long acting anti-cholinergic. If there is a greater degree of symptom severity (e.g. obstipation, nausea and vomiting, urinary retention) the medication will be discontinued. A clinic visit to the UNM Urogynecology Clinic will be arranged so that the subjects may be appropriately evaluated. If subjects report symptoms of concern to the medication counselor or other study personnel, subjects will be instructed to stop the medication and a clinic visit to the UNM Urogynecology Clinic will be arranged so that subjects may be appropriately evaluated. These measures will decrease the risk of harm from study participation. It is unlikely that these FDA approved, routinely prescribed medications will result in serious harm, but if significant events are reported, subjects will be evaluated and the PIs and Study Coordinator will generate a report and which will be distributed to the DSMB, HRPO (if meets HRPO reporting guidelines see 7.4) and NCCAM consistent with NCCAM policies (see 7.4). If the events are attributable to the medications, an action plan will be developed which may include protocol modification.

#### Bladder Catheterization

- *Dysuria*
- *Hematuria*
- *Urinary Tract Infection*

*Relevant background, management and modification of intervention or participant assessment for the above:* Subjects will have bladder catheters placed for their cystometric evaluation and those who participate in the fMRI portion of the study will also be catheterized to undergo bladder filling for the fMRI task. Cystometric evaluation is considered a routine standard of care procedure for women with urgency urinary incontinence. The risks of bladder catheterization, although unlikely, include dysuria, hematuria and urinary tract infection. A recent meta-analysis concluded that prophylactic antibiotics for complex bladder testing decreased significant bacteriuria with few side-effects, with a reported range of bacteriuria of 1-8% in the groups treated with antibiotic prophylaxis.<sup>46</sup>To

decrease infection risks of bladder catheterization during this study, prophylactic antibiotics will be given to all subjects prior to and the day of catheterization. Nitrofurantoin or Trimethoprim/Sulfamethoxazole will be administered prior to and the day of catheterization. Subjects allergic to these medications will be given appropriate alternate antibiotic prophylaxis. Prior to the procedure, the patient will be informed regarding the procedure protocol and potential discomforts and side-effects. Participants will be clearly informed of their right to withdraw from the study at any time. Catheterization will be performed using sterile technique by nursing staff whose standard practice is to perform this procedure. Additionally, subjects will have urine dipsticks checked at study entry and prior to bladder catheterization to ensure absence of urinary tract infections. Subjects noting persistent urinary tract infection symptoms following the tasks will have urine dipstick testing and a urine culture performed. Subjects with evidence of a urinary tract infection will be treated. UTI, hematuria and dysuria occurrence will be tracked and AEs reported to the DSMB. If these events occur in 10% or more subjects, the protocol will be reviewed and revised.

#### FMRI

- *Claustrophobia and Anxiety*
- *Dysuria, Hematuria and Urinary Tract Infection due to catheterization*
- *Unexpected Abnormality on MRI*

*Relevant background, management and modification of intervention or participant assessment for the above:*

These risks are small as MRIs are commonly performed clinical procedures without significant risk and without radiation exposure. To avoid the claustrophobia and anxiety which may occur with fMRI performance, subjects will be screened to rule out a history of claustrophobia prior to the MRI. Since the MRI may cause claustrophobia and anxiety from loud noises made by the machine (despite the fact that the MRN ambient scanner noise is below the current recommended guidelines), a two-way intercom system and a video monitoring system will provide continual monitoring of the subject's condition. If discomfort or concern is expressed or detected, the experiment will be stopped and the subject will be given the option to discontinue at any time. This event will be recorded. Please refer to evaluation and approach to events which may be associated with bladder catheterization described above. If an unexpected significant brain abnormality is found on fMRI the subject will be referred to her primary physician or other appropriate physician to evaluate the abnormality/finding.

#### Any of the following

- *Possible breach of confidentiality, stress, emotional distress and inconvenience:*

*Relevant background, management and modification of intervention or participant assessment for the above:*

These risks are possible with participation in any research study and will be minimized. In the unlikely circumstance that confidentiality is breached potential embarrassment associated with the diagnosis of urgency urinary incontinence may occur. This risk will be minimized by assigning a study number to each participant upon entry into the study and with the other measures described previously under Section III: Confidentiality in the DSMP. The stress, emotional distress and inconvenience will be minimized by recruiting, enrolling, evaluating and treating subjects in a private setting (private clinic exam rooms and private consultative, administrative, research and practitioners offices). The patient will be reassured that declining study participation will have no effect on their current or future clinical care. HIPAA consent will be signed in accordance with the UNMH HRPO (IRB) and the patient informed of the protections that HIPAA guarantees to the privacy of their health information. To further ensure the security of personal health information all data will be de-identified as described above. The database will be password protected and accessible only to research personnel. Only coded information will be entered into the database. All paper-based study subject folders will be kept in a locked cabinet in the Urogynecology research division administrative area. Therapies will be administered in a one on one setting. Appointments for therapy will be scheduled with efforts made to minimize inconvenience to the subject while maintaining study fidelity and completing counseling therapies within a two month window.

#### **7.1 Specification of Safety Parameters**

Events will be captured by research staff as described in the DSMB with particular attention to the following noted in the Frequency of Specific Events Table and are also explained in Section 7.4 and include;

1) potential breach of confidentiality 2) lack of adherence to functional MRI screening for metallic objects near MRI scanner or potential lack of adherence to pregnancy and UTI screening 3) request for MRI termination due to anxiety, claustrophobia while in the scanner 4) symptoms of dysuria, hematuria or urinary tract infections

associated with bladder catheterization 5) potential symptoms related to anticholinergic use such as severe nausea/vomiting or constipation, or inability to void 6) potential symptoms related to hypnotherapy sessions such as severe emotional upset which interferes with subject functioning 7) failure of subjects to comply with hypnotherapy CD/audio-recording instructions regarding prohibition of driving while listening to the recordings

## **7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters**

See section 7.0 above. As noted previously, the Frequency of Specific Events Table will be used to record the more significant potential symptoms/side effects of the interventions noted above and are further explained in Section 7.4 as well.

## **7.3 Adverse Events and Serious Adverse Events**

### **Definitions**

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with the use of the interventions being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram findings, etc.) or any combination of these. AEs will be recorded regardless of their relationship to the study intervention.

A Serious Adverse Event (SAE) is any untoward medical occurrence that results in death, is life threatening requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or congenital anomaly. Generally, an SAE can result in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

### **Classification of AE Severity**

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient some minor inconvenience and “severe” if it causes a substantial disruption to the patient’s well-being.

### **AE Attribution Scale**

AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, possibly related, probably related or definitely related to the study intervention.

**AE Guidelines** Adverse events will be reported in a manner consistent with the UNM HRPO (Human Research Protections Office) and NCCAM policies (See below).

## **7.4 Reporting Procedures**

*Monitoring of Adverse Events & Frequency of Periodic Observations & Reporting & Follow-up:* Adverse events will be monitored by spontaneous subject report and subject interviews and data review. At each clinic visit or follow-up telephone call, subjects will be asked to recall any adverse events since the time of their last contact (either via phone call, in-person clinic or study visit). The Study Coordinator (or her surrogate in her absence) will record the information using a standardized format and report the data to the PI’s. If the AE is a reportable event as defined by the UNM HRPO (i.e. meets all the following criteria; it was unanticipated, caused harm or placed a person at increased risk of harm, and was more likely than not to have been related to the research) it will also be reported to the UNM HRPO (see UNM HRPO “Event form” attached which must be signed by the PI or a designee in his/her absence and supporting documentation including the current consent) and the DSMB. The UNM HRPO will be notified of reportable events as soon as possible and within 5 days of the event date or

the “site awareness” date. AEs will be followed until they are resolved or considered stable, typically for one month, although this time will be extended to up to 4-6 months, depending on the instability of the event.

**SAEs** will be immediately (i.e. as soon as the Investigators or Study personnel are made aware that an SAE occurred) reported to the UNM IRB (HRPO) as per IRB guidelines and the NIH Project Officer and addressed by the DSMB if determined to be attributable to study participation (see SAEs below).

A Data Safety and Monitoring Board has been identified for this study. AE reports will be generated using standard forms, including the Adverse Event Case Report Form and Serious Adverse Event Case Report Form (see attached). The DSMB will meet quarterly for the first year and the DSMB will reassess and determine whether observations can be reviewed semi-annually thereafter. During the DSMP formal meetings the events will be reviewed. The severity of the event will be determined and an action plan to avoid recurrence of events (if found to be attributable to study participation) will be formulated and implemented. Research related adverse events will be reviewed and annual reports which include AE reports, subject enrollment/withdrawals and protocol violations will be generated for the University of New Mexico Health Sciences Center Human Research Protections Office (HRPO), Data Safety Monitoring Board and NCCAM/NCCAM Project Officer.

### **SAE Reporting**

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Data Safety Monitoring Board, the Human Research Protections Office (HRPO), and NCCAM in accordance with requirements.

- Unexpected fatal or life-threatening SAEs related to the interventions will be reported to the NCCAM Program Officer within 7 days (and will result in emergency convening of the Data Safety Monitoring Board). We will observe all UNM HRPO SAE reporting policies (see prior section). Other serious and unexpected AEs related to the intervention will be reported to the NCCAM Program Official within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Data Safety Monitoring Board, the UNM HRPO, NCCAM and other oversight organizations in accordance with their requirements. In the annual AE summary, the Independent Monitor Report (Data Safety Monitoring Board) will state that they have reviewed all AE reports.

### **7.5 Follow-up for Adverse Events**

AEs will be followed by the research team until they are resolved or considered stable, typically for one month, although this time will be extended to up to 4-6 months, depending on the instability of the event and will be tracked on the Adverse Event or SAE CRFs and the AE and SAE Tables by the PI and Research Coordinator.

### **7.6 Safety Monitoring**

The Co-PIs and NCCAM advisors have designated a Data Safety and Monitoring Board to perform an independent review of ongoing study progress and safety. The Data Safety and Monitoring Board for this study is comprised of Drs. Charles North, Cheryl Aine, Darren Braude, and Clifford Qualls who are not associated with this research project and thus work independently of the PIs, Drs Loren Ketai and Yuko Komesu, the Co-Principal Investigators. The DSMB members are not part of the key personnel involved in this grant. They are qualified to review the patient safety data generated by this study because of their unique expertise in the areas of radiology, statistics, urgency urinary incontinence, hypnotherapy and ethics. The CVs of all members of the Data Safety Monitoring Board are attached to the DSMP.

*Data Safety Monitoring Board:* This DSMB will consist of:

1. Charles North, MD

University of New Mexico Health Sciences Center

Professor of Family Medicine

Dr. North has experience in treating women with UUI as well as experience in ethical decision-making as Former Acting Head of U.S. Indian Health Services.

2.Cheryl J. Aine, PhD

University of New Mexico Health Sciences Center  
Research Professor, Department of Radiology

Dr. Aine has extensive experience in NIH-sponsored imaging studies with particular interest in neuro-imaging and would be appropriate for this proposal which includes brain imaging.

3.Darren Braude, MD, MPH, EMT-P

University of New Mexico Health Sciences Center  
Professor, Department of Emergency Medicine & Anesthesiology

Dr. Braude is a Clinical Hypnotherapist and his expertise in hypnosis makes him an appropriate DSMB member.

4.Clifford Qualls, PhD

University of New Mexico Health Sciences Center  
Professor Emeritus, Mathematics Statistics  
Dr. Qualls is a PhD statistician for the UNMH CTSC

## **8. Intervention Discontinuation**

Interventions will be discontinued if they result in substantial disruption to the subject's well-being with potential events listed in section 7.

Hypnotherapy will be discontinued for the individual subject if the subject complains of severe emotional upset attributed to hypnotherapy. Serious emotional upset includes inability to work or events that would necessitate evaluation by a physician or care provider. It is unlikely that this will occur. The potential for this occurring will be minimized by excluding subjects with a history of schizophrenia or untreated bipolar disorder and by having the hypnotherapist guide the sessions and terminate sessions if subjects are beginning to show signs of undue duress during hypnotherapy. However, though it is highly unlikely that hypnotherapy could potentially unmask or de-repress significant emotional upset (see Section 7) if a subject reports serious emotional upset from hypnotherapy, the intervention will be terminated and reported. The subject will continue to be followed clinically by the investigators until the symptoms resolve. If necessary, a Behavioral Health Consultation will be generated and will result in a meeting of the PIs and review of the issues surrounding its occurrence. The subject will be followed after intervention discontinuation (if it is found to be directly attributable to the intervention) until it resolves, typically within a month but potentially longer. The PIs and Study coordinator will generate a report, assess whether it was preventable, and develop an action plan to prevent recurrence including potential protocol revision and this will be reported immediately to the DSMB.

If serious medication related adverse events occur (significant urinary retention, debilitating constipation or nausea and vomiting) the medication will be discontinued. A clinic visit to the UNM Urogynecology Clinic will be arranged so that the subjects may be appropriately evaluated. If subjects report urinary retention or symptoms of a urinary tract infection or other symptoms of concern to the medication counselor or other study personnel, subjects will be instructed to stop the medication and a clinic visit to the UNM Urogynecology Clinic will be arranged so that subjects may be appropriately evaluated. Urinary retention will be evaluated by bladder catheterization or bladder scanning. These measures will decrease the risk of harm from study participation. It is unlikely that these routinely prescribed medications will result in serious harm, but if serious complications are reported, subjects will be evaluated and the PIs and Study Coordinator will generate a report and which will be given to the DSMB. If the events, such urinary retention or persistent urinary tract infections are directly attributable to the medications, an action plan will be developed which may include discontinuation of the treatment, potential protocol revision. The subject will be followed until the problem resolves, typically within a month but potentially longer.

Participants will continue to be followed with their permission if a study intervention is discontinued for the duration of the study (if the participant is willing). All data will continue to be collected (with the participant's permission) including questionnaires and voiding diaries.

## 9. Statistical Considerations

### 9.1 General Design Issues

This study includes

1. A single-blinded, randomized controlled trial (RCT) based on a non-inferiority design which compares hypnotherapy to pharmacotherapy in treating UUI.
  - Urge incontinent women (N=152) will be randomized to hypnotherapy or pharmacotherapy and evaluated at months 2, 6 & 12
2. Both a cross sectional study and RCT which will evaluate up to 80 of these women with UUI.
  - These women will undergo fMRI before treatment and their baseline imaging results will be compared to normative controls.
  - In addition, the UUI subjects participating in the fMRI will undergo imaging after treatment. The images of UUI subjects following treatment will be compared to their baseline images.

Specific Aims, Hypotheses and Outcomes;

Primary Outcomes:

1. Between group differences in change in UUI episodes for Specific Aim 1 at 2 month follow-up based on 3 day voiding diaries
2. Between group differences in change in activation of limbic cortex and brain connectivity following treatment for Specific Aim 2

Secondary Outcomes:

1. Between group differences in change in UUI episodes for Specific Aim 1 from baseline to follow-up at both 6 and 12 months based on 3 day voiding diaries.
2. Between group differences in change in pad counts, voiding frequency and cure (resolution) of UUI on voiding diary for Specific Aim 1 at 2, 6 and 12 month follow-up as well as “durable cure” (resolution of UUI on all follow-up diaries at 2, 6 & 12 months)
3. Between group differences in the follow-up expectation question and between group differences in questionnaire change scores (the OAB-qSF, ISI, PISQ-12, Global questionnaire, CRADI-8, IBS Module, IC questionnaire) for Specific Aim 1 at 2, 6 and 12 month follow-up
4. Baseline differences in activation of the limbic cortex and brain connectivity in women with UUI compared to normative controls for Specific Aim 2

1. Specific Aim 1: Determine whether a mind/body therapy (hypnotherapy) is as, or is more effective and durable, in treating urgency urinary incontinence (UUI) than a non-mind/body treatment (pharmacotherapy)

*Hypothesis: Among patients with urgency urinary incontinence, hypnotherapy ameliorates abnormal perception of bladder distension outside the hypnotic state and thereby diminishes symptoms of urgency and decreases incontinence as effectively as (or more effectively than) pharmacotherapy*

Clinical response of UUI subjects to Hypnotherapy compared to Pharmacotherapy Outcomes:

The primary outcome for the analysis of Objective 1 will be change in UUI episodes for the hypnotherapy group compared to the pharmacotherapy group at 2 months based on 3 day voiding diaries.

Secondary outcome measures of Objective 1 will include differences between the hypnotherapy and pharmacotherapy groups regarding change in UUI episodes at 6 and 12 months, and change in urinary frequency, pad counts and cure (defined as zero UUI episodes) on voiding diaries at 2, 6 and 12 month follow-up, and “Durable Cure” of UUI (defined as zero UUI episodes on all voiding diaries which include the 2, 6 and 12 month diaries). Secondary outcomes will also compare group differences in expectation attainment (i.e. differences in answers to follow-up Expectation question) and between group differences in questionnaire change scores [OAB-qSF, ISI, Global (PPBC) questionnaires and Sexual function scores (PISQ-12) in those women willing to answer the PISQ-12] while accounting for covariates such as medical history and demographic variables as well as pain/interstitial cystitis (based on VAS pain scale and PBIC-SS) or bowel abnormalities

(based on the CRADI-8 questionnaire and IBS Module) and evaluating change in the CRADI-8, IBS Module or PBIC-SS questionnaires if adequate numbers of subjects are found to have bowel or IC abnormalities.

A randomized, single-blinded, parallel group active controlled trial using a non-inferiority design was chosen. The non-inferiority design was chosen as the control group will be taking an intervention, anti-cholinergics, which is the standard of standard of care for women with UI; we wished to evaluate whether a novel mind-body treatment, hypnotherapy, was at least as successful in treating UI as the standard therapy. Both the primary and secondary outcome measures are validated and reliable measures which accurately reflect UI severity. The International Consultation on Incontinence (ICI) recommends that all incontinence research include validated questionnaires and voiding diaries.<sup>1</sup> The voiding diary adheres to ICI recommended parameters with an intra-class correlation coefficient=.76 and moderate-excellent convergent validity with patient recall as measured by Spearman's rank correlation=.7.<sup>8</sup> The most commonly used primary outcome measure in randomized controlled trials, as noted in a recent AHRQ Review, is the 3-7day voiding diary.<sup>84</sup> As 3 day voiding diaries are as valid as 7 day diaries and are far less burdensome to patients, 3 day diaries will be used in this study.<sup>8</sup> The OABq-SF, validated for overactive bladder, discriminates between patients who are continent and incontinent.<sup>15</sup> Internal consistency of its symptom bother subscale (.86) and its quality of life subscale (.89-.96) are high. It received a Grade A recommendation from the ICI as it met content and construct validity, internal consistency, test-retest reliability, and responsiveness standards.<sup>14</sup> The Global scale, the PPBC, has demonstrated good construct and discriminant validity and responsiveness measured against UI episodes (Spearman correlation co-efficients .21-.37,  $P<.0001$ ) and is more specific for use in patients with Urgency Urinary Incontinence compared to many other global indices.<sup>84,85</sup> This scale is important as Global ratings may provide the single best disease-related measure of change from the individual's perspective.<sup>19</sup>

2. Specific Aim 2: Determine whether hypnotherapy treatment of UI (urgency urinary incontinence) is associated with greater modification of brain activation and connectivity on functional MRI than that which occurs following pharmacotherapy.

*Hypothesis 2.1. Patients with urgency urinary incontinence will exhibit increased activation within portions of the limbic cortex (anterior cingulate cortex and insula) during bladder distension relative to healthy controls. Patients will also exhibit an abnormal pattern of functional connectivity within the limbic system.*

*Hypothesis 2.2. Among patients with urgency incontinence, hypnotherapy will decrease hyper-activation of the limbic cortex in response to bladder distension and/or modulate functional connectivity within the limbic system. Moreover, normalization of hyper-activation and connectivity will be greater in hypnotherapy compared to pharmacotherapy*

Baseline (pre-treatment) differences between subjects with UI and healthy controls with respect to task related limbic system activity and resting connectivity in subjects:

Primary outcome measures for Objective 2.1 will be UI subject versus normal control differences in task related activation of the insula and anterior cingulate cortex and differences in resting functional connectivity between these groups. Task related fMRI signals have been used extensively in the investigation of both motor and cognitive tasks and have been found to correlate well with other indices of neuronal function and neuronal spatial location within the brain.<sup>7</sup> More recently fMRI measurement of resting functional connectivity has been shown to be powerful tool for the investigator of neuronal function and localization. By using spontaneous rather than event related signal this technique results in a threefold increase in signal to noise. Resting functional activity has successfully demonstrated group differences between controls and numerous disease states, including differences between patients with chronic pain and healthy controls.<sup>28</sup>

Post-treatment differences between subjects receiving hypnotherapy versus subjects receiving pharmacotherapy with respect to task related limbic system activity and resting connectivity:

Primary outcome measures for Objective 2.2 will be pharmacotherapy treated subject versus hypnotherapy treated subject change in task related activation of the insula and anterior cingulate cortex and change in resting functional connectivity between these groups. The test-retest reliability of fMRI results have been evaluated in multiple settings including within multicenter research consortiums.<sup>82</sup> Assessment of the reliability of brain activation within regions of interest has shown intra-class correlation coefficients frequently greater than 0.8.<sup>30</sup> Test-retest reliability has also been shown to be preserved over a one year time span.<sup>3</sup>

## 9.2 Sample Size and Randomization

*Power Analysis/ Sample Size Calculation for Clinical RCT Specific Aim 1:* We performed sample size calculations for change in UUI episodes and change in OABq-SF scores based on our pilot data & urgency incontinence literature.<sup>11,16,52</sup> The study design will use a non-inferiority design to compare the primary outcome (change in UUI episodes in the hypnotherapy versus pharmacotherapy groups). With respect to the outcome variable of percent reduction in UUI episodes as determined by bladder diaries, we will use a one-sided non-inferiority test at level  $\alpha = 0.25$  and a non-inferiority margin of 5%. If  $\mu_h$  is the population mean percent reduction in incontinent episodes for the hypnotherapy group, and  $\mu_m$  is the population mean percent reduction in incontinent episodes for the medications group, we will then test  $H_0: \mu_h - \mu_m \leq -5$  against the one-sided alternative  $H_A: \mu_h - \mu_m > -5$  using significance level 0.025. If the null hypothesis is rejected then we may conclude hypnotherapy is not inferior to medication therapy, on average, by more than 5%, and in fact may be superior to medication therapy, with respect to percent reduction in incontinent episodes. The test may be performed by computing the lower 97.5% one-sided confidence bound for  $\mu_h - \mu_m$ . If the lower confidence bound exceeds -5% we will conclude non-inferiority of hypnotherapy. Should that lower bound exceed zero we will conclude superiority. Assuming a subject drop-out, withdrawal and missing data rate as high as 33%, 52 subjects will be available for analysis in both hypnotherapy and medications groups. If  $\mu_h - \mu_m \geq 9\%$ , this sample size would provide power  $\geq 80\%$  for the non-inferiority test. Rigorous efforts will be made to reach an achieved attrition rate of 20-25%, such that approximately 60 subjects would be available for analysis in each group. This would allow for detecting non-inferiority if the actual  $\mu_h - \mu_m \geq 8\%$ . If the attrition rate at 1 year follow-up is  $< 20\%$ , randomization of 152 subjects will allow us to detect even smaller inter-group differences than quoted previously.

*Power Analysis/ Sample size Calculation for fMRI for Hypothesis 2.1 (Normative controls vs. urgency incontinence subjects):* Regions of interest containing the insula and anterior cingulate cortex will be analyzed in keeping with our a priori hypothesis using two way ANCOVA with group as the between subject's factor and age as a covariate. Pre-treatment  $\beta$  weights for both bladder filling and urgency regressor effect on anterior cingulate cortex and insula signal among normative subjects will be compared to the effect on signal in urgency incontinence subjects. The planned study size allows detection of differences between groups with an effect size  $> 0.8$  with power of 0.8, smaller than the observed effect size in our pilot study.<sup>43</sup> The effect size observed in our pilot study (Cohen's d ranged from 0.8 to 1.5) suggests that the study will be adequately powered (greater than 0.8) to reject the null hypothesis at an  $\alpha=0.05$ . In addition to analysis of prior regions of interest, group wise whole brain contrast will also be performed using an identical statistical model. False positives will be corrected at a significance threshold corresponding to  $p < .005$  applied in combination with a minimum cluster size threshold of 32 native voxels ( $p < 0.05$ ), parameters derived from 10,000 Monte Carlo simulations.<sup>80</sup> Analysis of between group differences in functional connectivity will be performed in a similar fashion to that used to analyze brain activation evoked by bladder filling and emptying. The large observed effect size in our preliminary data ( $> 3$ ) suggests that the sample size used for proposed analysis of evoked potentials will be more than adequate. Although the principal purpose of this analysis is to further explore the pathophysiologic underpinnings of UUI within the brain, we will also explore the use of evoked potentials and functional connectivity as a biomarker for UUI. Towards that end we will construct receiver operator curves (ROCs) based on fMRI output from controls and patients with UUI.

*Statistical Analysis 2.2 Pre- and Post-Treatment measurements in patients with UUI:* Prior functional MRI analysis during the hypnotic state has shown complete suppression of anterior cingulate cortex activation in response to pain.<sup>55</sup> However, the magnitude of suppression of anterior cingulate cortex or insula signal outside the hypnotic state has not been studied. Current study size will be able to detect differences between pre and post treatment signal within a treatment group with an effect size of approximately 0.5 and a power of 0.8. Minimal effect size would be approximately equivalent to a 60% decrease in the excess (above normative control) anterior cingulate cortex and insula signal. We predict a main effect of time, suggesting that both treatments are effective in reducing activity within the anterior cingulate cortex and insula. However, we also predict a significant Group x Time interaction, indicating that that change in activity will be greater for the hypnotherapy relative to the pharmacotherapy group. Minimum detectable effect size for the Group X Time interaction is 0.7 with power of 0.8 and  $\alpha$  of 0.05. Similar to brain activation, no prior data is available in the literature regarding the expected change in waking state connectivity following hypnotherapy. Current study size will be able to detect within-group differences between pre and post treatment signal with a minimal effect size of approximately 0.5 and a power



of 0.8, much lower than the observed effect size of  $>3$  in our pilot study. The minimum effect size would be reached with a 15% decrement in anterior cingulate cortex to insula connectivity. As for evoked activity we predict both a main effect of time, and predict a significant Group x Time interaction, indicating that change in functional connectivity will be greater for the hypnotherapy relative to the pharmacotherapy group. Minimum detectable effect size for the Group X Time interaction is 0.7 with power of 0.8 and alpha of 0.05. This minimum effect size will be reached when between group differences in anterior cingulate cortex to insula connectivity are  $\geq 30\%$ .

The principal purpose of this analysis will be to explore the mechanism of action of hypnotherapy when used to treat UUI, using pharmacotherapy as a control treatment that is not expected to exert its therapeutic effect via the brain. In addition we will explore the utilization of evoked activity and functional connectivity as biomarkers by correlating changes in these fMRI parameters with physiologic outcome measures, specifically UUI episodes. We understand that there is currently insufficient literature to determine the optimal method of assessing this correlation in the setting of a non-inferiority study design, and will look towards OCRA guidance on this aspect of the analytic plan in the future.

## **Treatment Assignment Procedures**

### *Randomization to treatment*

Study participants will be randomized to either pharmacotherapy or hypnotherapy groups using a computer-generated randomization scheme in varying permuted block sizes of 4-8. SAS 9.3<sup>®</sup> Proc-Plan software will create a randomization scheme of varying permuted block sizes of 4-8 to avoid severe inequality of group sizes for this 2 arm study. Subjects will be stratified based on fMRI performance and UUI severity ( $< 4$  UUI episodes vs.  $\geq 4$  UUI episodes on 3 day voiding diaries). UUI severity should be comparable in both groups because it is a potential risk factor for treatment failure. UUI severity will be defined by UUI frequency. Burgio<sup>83</sup> identified risk factors for unsuccessful behavioral treatment of UUI. Women with  $> 10$  UUI episodes on baseline voiding diaries were much less likely to be completely continent after behavioral treatment. For purposes of this study, on a 3 day diary approximately 4 UUI episodes would be a potential risk factor for treatment failure and stratification will be performed in order to avoid UUI severity imbalances between the treatment groups. fMRI stratification will be performed to ensure appropriate representation of both treatment groups in the fMRI study.

The UNMH CTSC biostatistics core will generate the computer randomization scheme for the study. Dr. Ronald Schrader will generate the scheme before enrollment begins and will be blinded to subject allocation after the RCT is initiated; he will have no patient contact, research personnel will not disclose unique patient identifiers to him, and he will remain blinded to patient randomization until study completion. Trial randomization codes will be maintained by the CTSC and Dr. Clifford Qualls (who is uninvolved with study analysis) will have the ability to break the blind. Breaking blinding is planned when all subjects in the RCT (N=152) have completed 12 month follow-up and when data collection and data quality checking have been completed. In the extremely unlikely event that the study is terminated or discontinued early due to excessive numbers of unanticipated and severe AEs determined to be warranted by the DSMB, the blind will be broken earlier than planned. The latter will occur after agreement by NCCAM and the DSMB, in which case the CTSC biostatistics office will be notified and the blind will be broken.

Group assignments will be placed in opaque, sealed envelopes by an individual otherwise unassociated with the study. The envelopes will be opened and subjects will be randomized only after subjects have signed informed consent and completed baseline evaluations. Investigators involved in interpreting fMRIs, investigators participating in the RCT, study personnel performing data entry and the study statistician will be blinded to knowledge of subjects' treatment groups. Investigator blinding will only be breached if a subject suffers an unexpected clinical event and investigator knowledge of the subject's treatment is essential to providing standard of care. Subjects cannot be blinded to treatment interventions as it will be obvious to them whether or not they are undergoing hypnotherapy or taking medications.

## **9.3 Definition of Populations (ITT versus Per Protocol)**

### **Intention to Treat:**

The primary analysis for the RCT will be an Intention to Treat Analysis. Outcomes for the RCT will be performed comparing subjects randomized to hypnotherapy compared to pharmacotherapy who have at least baseline efficacy assessments. Subjects who are missing, non-compliant or who use off-protocol therapies will still be analyzed in their assigned treatment groups in the ITT. For the primary analysis, any missing observations will be treated as missing at random. We will also use both parametric mixed models and longitudinal semi-parametric regression model to explore and compare differences over time of urinary incontinent episodes in the two arms

#### **Per Protocol Analysis:**

A secondary analysis for the RCT will be a per protocol analysis, evaluating outcomes for subjects based on therapy compliance and use of off-protocol therapies as well as performing sensitivity analysis for missing values

#### *Non-adherence/Non-Compliance to treatment protocol at 2 month follow-up of the study:*

##### *Definition Non-adherence/Non-Compliance:*

- Medication group: Subjects state 'no' on the Pharmacotherapy Compliance form (question #1) that they are no longer taking their medications at 2 month follow-up
- Attendance of < 60% of hypnotherapy appointments

Measures taken to improve non-adherence during 1st 12 weeks of the study: Data on adherence to the treatment protocol will be collected weekly during the treatment phase of the study by research staff and reviewed monthly by the PI. Data on adherence will be reviewed at each of the DSMB meetings (described above). Adherence of participants randomized to medications will be evaluated by assessing their answer to question #1 on the Pharmacotherapy Compliance form (see above). Available data on the use of anti-cholinergics for urgency urinary incontinence suggests an overall non-compliance or withdrawal rate of 30% in randomized controlled trials and rates below 45% at 1 month and 13% at 1 year in clinical practice. If average adherence falls below the suggested rate of 60% a conference call will occur for study investigators to discuss methods for improving adherence without affecting the integrity of the study. However, given the data regarding anti-cholinergic side effects, it is quite possible that this non-adherence rate is not changeable. Protocol adherence in subjects randomized to hypnotherapy will be measured by monitoring compliance in keeping hypnotherapy appointments. If adherence of hypnotherapy subjects falls below a suggested rate of less than 60%, a conference call for study personnel to discuss methods for improving treatment adherence will occur.

#### *Non-compliance/Non-Compliance or use of off-protocol therapies at 6, 12 month follow-up visits*

##### *Definition of Non-adherence/Non-Compliance at 6 & 12 month follow-up:*

- Medication group: Subjects state 'no' on the Pharmacotherapy Compliance (question #1) form that they are no longer taking their medications at 6 or 12 month follow-up
- Hypnotherapy group: Subjects who state 'no' on the Hypnotherapy Compliance form (question #1) that they are not listening to their hypnotherapy CDs or practicing self-hypnosis at 6 or 12 month follow-up

##### *Definition of use of off-protocol treatments*

- Subjects use other treatments for UUI such as sacral neuromodulation, intravesical botox in the last 12 months or other UUI medications (such as Toviaz®/Fesoterodine or Sanctura®/Tropium or Vesicare®/Solifenacin or Enablex®/Darifenacin or Myrbetriq®/Mirabegron)
- Subjects use acupuncture to specifically to treat UUI
- Subjects use herbal remedies specifically to treat UUI

##### *Analysis of non-compliance or use of off-protocol treatments:*

Subjects who are non-compliant or use off-protocol therapies will still be analyzed in their assigned treatment groups in the ITT analysis. When subjects implement off-protocol therapies, we will examine the sensitivity of the per protocol analyses in two ways. First, we will modify the models to incorporate a time-varying treatment parameter that can be used to examine the effect of received treatment. Second, we will censor all measurements after they receive alternative treatment, and then impute all censored measurements using multiple imputations based on information collected from those who do not switch. Non-Compliance will be analyzed in the per-protocol analysis first as a categorical variable (yes/no) in its relationship to the outcome(s)

and will then be evaluated as a continuous variable (i.e. times self-hypnosis practiced or CD/digital recording used) in its relationship to the outcome.

#### Missing Data:

Standard procedures will be used to ensure that data are as complete and accurate as possible. In order to decrease missing data, data collection forms will be designed for recording measurements and the Redcap (Research Electronic Data Capture) System, as recommended by the UNMH CTSC, will be used by the research staff for data management. Study personnel will check the data collection forms for completeness before study participants leave the clinic so that missing clinical information may be addressed while study participants are still in the clinic. Downloads will be performed to check for missing values and skipped entries using SAS® programming and will be designed to avoid skipped entries and allow flagging of missing data. Our goal is to maintain a loss to follow-up rate less than 10% though we will conservatively plan on a loss to follow-up rate of 20%. Our goal is to maintain a missing data rate of less than 10% overall.

We anticipate that missing data will be generated in two primary ways; 1) Small numbers of subjects may withdraw consent or be lost to follow-up and will not have any measurements after their withdrawal. In this case, the study will be missing all data and these will be censored observations. The missing data may fall across the spectrum from missing completely at random to missing not at random 2) Subjects may fail to provide data at a specific follow-up time due to unforeseen life-events (illness, family emergencies) that do not allow them to provide assessments within the allowable window. The missing data from this second group will follow an intermittent pattern. Again, the missing data may fall across the spectrum from missing completely at random to missing not at random

We will use two general strategies for assessing the sensitivity of both primary and secondary analyses to missing at random and missing completely at random assumptions. First, for individuals that withdraw from the study or have missing visits, we will collect information on the reasons for those missed visits. That information, coupled with data collected from earlier visits will be used to develop comparisons of the two treatment arms using pattern mixture models. For the second approach, we will use multiple imputation based on a model conditional on baseline covariates, treatment group, and all previous measures. Separate imputation models will be used for the two groups.

## **9.4 Interim Analyses and Stopping Rules**

### **Stopping Rules**

This is a low risk study as both interventions are low risk; pharmacotherapy is a standard, accepted treatment of UUI and hypnotherapy is considered a low risk intervention as hypnosis can only occur in subjects who allow themselves to be hypnotized (i.e. the hypnotic state cannot be forced upon individual). Nonetheless, in the unlikely event that the following situations occur, the study will be stopped prior to completion if: (1) any of the interventions are associated with SAEs attributable to the interventions that call into question the safety of the interventions (likelihood is extremely low) (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints (likelihood is extremely low) (3) any new information becomes available during the trial that necessitates stopping the trial (likelihood is extraordinarily low).

In the unlikely event that >33% of study subjects report that they experience serious emotional upset from study participation the study will be suspended and a review will occur. Serious emotional upset includes inability to work or events that would necessitate evaluation by a physician or care provider. It is unlikely that this will occur as we have had 0/17 subjects in our pilot study evaluating hypnotherapy treatments in OAB subjects report physical or emotional upset from study participation. However, it is highly unlikely that hypnotherapy could potentially unmask or de-repress significant emotional upset (e.g. hysteria, uncontrollable anger or hostility) in subjects. The potential for this occurring will be minimized by excluding subjects with a history of schizophrenia or untreated bipolar disorder and by having the hypnotherapist guide the sessions and terminate sessions if subjects are beginning to show signs of undue duress during hypnotherapy. A report of a subject experiencing serious emotional upset from study participation will result in a meeting of the PIs and review of the issues surrounding its occurrence. The PIs and Study coordinator will generate a report, assess whether it was

preventable, and develop an action plan to prevent recurrence including potential protocol revision and this report will be given the DSMB. The likelihood of this occurring is very small. Sporadic occurrence of emotional upset is always possible in any setting, and if an individual treated with hypnotherapy notes this occurrence which she attributes to hypnotherapy, the intervention will be terminated. However, we believe that if a third of subjects complain of this issue, the study should be halted until the circumstances surrounding its occurrence are investigated. Other hypnotherapy studies have not reported this occurring; however, we believe that it is prudent to consider this as a possibility and to prepare for it as a possibility, although highly unlikely. The study would also be stopped if there were statistically significant differences in SAEs (as defined in section 7.3) definitely attributable to the interventions (hypnotherapy or pharmacotherapy). The medications in the pharmacotherapy arm, considered standard of care treatments, have undergone rigorous FDA approval, and it would be highly unlikely that these events would occur.

## 9.5 Outcomes

Outcomes documentation will not be reviewed and adjudicated by a committee. Outcomes will be analyzed by the Investigators and Study Statistician, Dr. Ronald Schrader, after the study is completed and the blind is broken using standard SAS® software on the Redcap® database maintained in a fashion consistent with UNM HRPO policy.

### 9.5.1 Primary Outcome

*Specific Aim 1:* Determine whether a mind/body therapy (hypnotherapy) is as, or is more effective and durable, in treating urgency urinary incontinence (UUI) than a non-mind/body treatment (pharmacotherapy)

The primary outcome for the analysis of Objective 1 will be change in UUI episodes based on 3 day voiding diaries for the hypnotherapy group compared to the pharmacotherapy group at 2 month follow-up (See flow Diagrams Section 5. “Study Interventions”)

*Specific Aim 2:* Determine whether hypnotherapy treatment of UUI (urgency urinary incontinence) is associated with greater modification of brain activation and connectivity on functional MRI than that which occurs following pharmacotherapy.

*Hypothesis 2.2.* *Among patients with urgency incontinence, hypnotherapy will decrease hyper-activation of the limbic cortex in response to bladder distension and/or modulate functional connectivity within the limbic system. Moreover, normalization of hyper-activation and connectivity will be greater in hypnotherapy compared to pharmacotherapy*

The primary outcome is to evaluate whether UUI subjects treated with hypnotherapy have decreased hyper-activation of the limbic cortex (ACC and insula) in response to bladder distention and/or modulation in functional connectivity within the limbic cortex in response to bladder distension compared to subjects treated with pharmacotherapy. This will be obtained after the subjects finish their 8 weeks of either pharmacotherapy or hypnotherapy (Visit 12; see flow Diagrams Section 5. “Study Interventions”)

### 9.5.2 Secondary Outcomes

*Specific Aim 1:* Determine whether a mind/body therapy (hypnotherapy) is as, or is more effective and durable, in treating urgency urinary incontinence (UUI) than a non-mind/body treatment (pharmacotherapy)

This Aim’s primary outcome: will be to compare between group difference in change in UUI episodes at 2 months. Secondary outcomes will be to; determine whether a mind/body therapy (hypnotherapy) is as, or is more effective and durable, in treating urgency urinary incontinence (UUI) than a non-mind/body treatment (pharmacotherapy) comparing change in UUI episodes at 6 and 12 months as well as comparing between group changes in urinary frequency and pad counts recorded on 3 day voiding diaries at 2,6 and 12 months, difference in “cure” in UUI episodes (defined as complete resolution of UUI, i.e. 0 UUI episodes, on voiding diaries at 2,6 and 12 months) and “durable cure” (defined as complete resolution of UUI on all follow-up voiding diaries at 2, 6 and 12 months), differences in expectation attainment (i.e. between group differences in follow-up Expectation question) and differences in questionnaire change scores [OAB-q SF, ISI, Global (PPBC) questionnaire scores and change in sexual function based on PISQ-12 scores]. Additionally, we will evaluate the baseline occurrence of concomitant syndromes such as irritable bowel syndrome and painful bladder syndrome in this population of

women with UUI based on the medical history and CRADI-8 and IBS Module and IC questionnaires. We will explore whether there is a difference in pain and IC symptoms following treatment if there are sufficient numbers of women with bowel abnormalities and IC at baseline.

**Specific Aim 2:** Determine whether hypnotherapy treatment of UUI (urgency urinary incontinence) is associated with greater modification of brain activation and connectivity on functional MRI than that which occurs following pharmacotherapy.

**Hypothesis 2.1.** *Patients with urgency urinary incontinence will exhibit increased activation within portions of the limbic cortex (anterior cingulate cortex and insula) during bladder distension relative to healthy controls. Patients will also exhibit an abnormal pattern of functional connectivity within the limbic system.*

This Aims' secondary outcome will be to evaluate differences in brain activation of the limbic cortex and brain connectivity at baseline between women with UUI and normative controls.

## **9.6 Data Analyses**

**Specific Aim 1:** Determine whether a mind/body therapy (hypnotherapy) is as, or is more effective and durable, in treating urgency urinary incontinence (UUI) than a non-mind/body treatment (pharmacotherapy)

**Statistical Analysis:** Improvement between hypnotherapy and controls will be compared at baseline and follow-up at 2, 6, 12 months. Because of the possibility that a number of subjects may be cured (i.e. report "0" urgency incontinence episodes) at follow-up on voiding diary, we will use a zero inflated Poisson (ZIP) generalized linear mixed model for the analysis and compare groups' urgency incontinence episodes. The ZIP model analysis is proposed because the data are expected to be relatively low counts with the potential of a large numbers of zeroes, particularly at 2 and 6 months, in excess of those allowed by the Poisson. Simple conversion to percent change will not correct the discrete nature of the data ("cures" become 100 percent change rather than 0 UUI count at 2 months), and standard least squares methods will not be appropriate. If there is no inflation at 0, i.e. standard Poisson regression is appropriate, then the associated log-linear model yields percent change as a natural parameter (by exponentiating the group effect). If there is significant inflation at 0, the confidence interval for percent change in the mean will be constructed by combining the two portions of the model with standard error estimated by the delta method, and checked via bootstrap methods. We will be able to derive mean UUI episodes as well as mean % change in UUI episodes following ZIP model analyses. All other parameters, which are normally distributed or continuous variables, will be compared using a linear mixed model analysis. It is unlikely that there will baseline differences between groups, given that this is a randomized controlled trial. If baseline differences between groups are found (e.g. incontinence duration, coexisting illnesses, prior treatment), appropriate variables will be added to the analysis as covariates. We will include pre-treatment patient expectations and hypnotic susceptibility as covariates in the analysis and determine if they are independent predictors of treatment response. We will not exclude subjects based on hypnotic susceptibility to increase the generalizability of our findings. We anticipate subjects' pre-treatment expectations will be an independent predictor of improvement in urgency incontinence & questionnaire scores (the previously determined sample size is adequately powered to find a relatively small partial  $R^2$  of .05<sup>13</sup> between expectations and outcomes). The primary outcome measure will be change in UUI episodes from baseline to follow-up with a between group comparison, and not "cure". However, the term "cure" may be used for secondary analyses. As such, our definition of "cure" will be: absence of UUI episodes recorded on voiding diaries at 2, 6 and 12 month follow-up. Primary analyses will be performed using intention to treat. A per protocol analysis will also be performed; those who did not comply with the study interventions, extensively used other concomitant treatments known to improve UUI (e.g. used other UUI medications, underwent sacral neuro-modulation), or missed multiple treatment sessions will be considered to have been off protocol subjects. Similar analyses will be performed comparing group differences in change in questionnaire scores while accounting for covariates such as pain/interstitial cystitis (based on VAS pain scale and IC questionnaire) or bowel abnormalities (based on the CRADI-8), medical history and demographic variables (based on the medical history and demographic sheets) on the outcomes.

**Specific Aim 2:** Determine whether hypnotherapy treatment of UUI (urgency urinary incontinence) is associated with greater modification of brain activation and connectivity on functional MRI than that which occurs following pharmacotherapy.

Hypothesis 2.1. Patients with urgency urinary incontinence will exhibit increased activation within portions of the limbic cortex (anterior cingulate cortex and insula) during bladder distension relative to healthy controls. Patients will also exhibit an abnormal pattern of functional connectivity within the limbic system.

Hypothesis 2.2. Among patients with urgency incontinence, hypnotherapy will decrease hyper-activation of the limbic cortex in response to bladder distension and/or modulate functional connectivity within the limbic system. Moreover, normalization of hyper-activation and connectivity will be greater in hypnotherapy compared to pharmacotherapy.

*Statistical Analysis of 2.1 Normative controls vs. urgency incontinence subjects:* Regions of interest containing the insula and anterior cingulate cortex will be analyzed in keeping with our a priori hypothesis using two way ANCOVA with group as the between subject's factor and age as a covariate. Pre-treatment  $\beta$  weights for both bladder filling and urgency regressor effect on anterior cingulate cortex and insula signal among normative subjects will be compared to the effect on signal in urgency incontinence subjects. The planned study size allows detection of differences between groups with an effect size  $>0.8$  with power of 0.8, smaller than the observed effect size in our pilot study.<sup>43</sup> The effect size observed in our pilot study (Cohen's  $d$  ranged from 0.8 to 1.5) suggests that the study will be adequately powered (greater than 0.8) to reject the null hypothesis at an  $\alpha=0.05$ . In addition to analysis of prior regions of interest, group wise whole brain contrast will also be performed using an identical statistical model. False positives will be corrected at a significance threshold corresponding to  $p < .005$  applied in combination with a minimum cluster size threshold of 32 native voxels ( $p < 0.05$ ), parameters derived from 10,000 Monte Carlo simulations.<sup>80</sup> Analysis of between group differences in functional connectivity will be performed in a similar fashion to that used to analyze brain activation evoked by bladder filling and emptying. The large observed effect size in our preliminary data ( $>3$ ) suggests that the sample size used for proposed analysis of evoked potentials will be more than adequate.

Although the principal purpose of this analysis is to further explore the pathophysiologic underpinnings of UUI within the brain, we will also explore the use of evoked potentials and functional connectivity as a biomarker for UUI. Towards that end we will construct receiver operator curves (ROCs) based on fMRI output from controls and patients with UUI.

*Statistical Analysis 2.2 Pre- and Post-Treatment measurements in patients with UUI:* Efficacy of hypnotherapy and pharmacotherapy on anterior cingulate cortex and right insula activation will be compared using a 2x2 (Group x Time) mixed model ANCOVA to correct for potential differences in group characteristics (e.g. age). Analysis of treatment effect will be focused on the anterior cingulate cortex and insula based on preliminary data that suggests the effect size for change in activation will be highest in these regions. Prior functional MRI analysis during the hypnotic state has shown complete suppression of anterior cingulate cortex activation in response to pain.<sup>55</sup> However, the magnitude of suppression of anterior cingulate cortex or insula signal outside the hypnotic state has not been studied. Current study size will be able to detect differences between pre and post treatment signal within a treatment group with an effect size of approximately 0.5 and a power of 0.8. Minimal effect size would be approximately equivalent to a 60% decrease in the excess (above normative control) anterior cingulate cortex and insula signal. We predict a main effect of time, suggesting that both treatments are effective in reducing activity within the anterior cingulate cortex and insula. However, we also predict a significant Group x Time interaction, indicating that that change in activity will be greater for the hypnotherapy relative to the pharmacotherapy group. Minimum detectable effect size for the Group X Time interaction is 0.7 with power of 0.8 and  $\alpha$  of 0.05. Simple effects tests will also be conducted to ensure that randomization to treatment arm was successful (i.e. no differences in baseline activity across the two groups).

Similar analyses will be conducted to evaluate the effect of treatment on functional connectivity. No prior data is available in the literature regarding the expected change in waking state connectivity following hypnotherapy. Current study size will be able to detect within-group differences between pre and post treatment signal with a minimal effect size of approximately 0.5 and a power of 0.8, much lower than the observed effect size of  $>3$  in our pilot study. The minimum effect size would be reached with a 15% decrement in anterior cingulate cortex to insula connectivity. As for evoked activity we predict both a main effect of time, and predict a significant Group x Time interaction, indicating that change in functional connectivity will be greater for the hypnotherapy relative to the pharmacotherapy group. Minimum detectable effect size for the Group X Time interaction is 0.7 with power

of 0.8 and alpha of 0.05. This minimum effect size will be reached when between group differences in anterior cingulate cortex to insula connectivity are  $\geq 30\%$ .

The principal purpose of this analysis will be to explore the mechanism of action of hypnotherapy when used to treat UUI, using pharmacotherapy as a control treatment that is not expected to exert its therapeutic effect via the brain. In addition we will explore the utilization of evoked activity and functional connectivity as biomarkers by correlating changes in these fMRI parameters with physiologic outcome measures, specifically UUI episodes. We understand that there is currently insufficient literature to determine the optimal method of assessing this correlation in the setting of a non-inferiority study design, and will look towards OCRA guidance on this aspect of the analytic plan in the future.

*Anticipated/Expected Outcomes:* Results from this study should confirm the differences between normative and urgency incontinence subjects with respect to limbic system evoked activation and functional connectivity. Confirmation of abnormal functional connectivity in urgency incontinence subjects during the resting state would be a particularly important contribution to the study of functional disorders in general. Abnormal resting connectivity data does not require that data be acquired and temporally linked to a performance of a task while in the MRI scanner making data acquisition less technically demanding. Abnormal resting connectivity has thus far only been observed in fibromyalgia but if shown to be more widely present among functional disorders could prove a diagnostic tool and/or target of new therapies. Demonstration that hypnotherapy's impact on brain activation and connectivity extends past the hypnotic state and persists during wakefulness would allow treatment effects of hypnotherapy, and perhaps other mind/body therapies, to be assessed temporally distant from the time of therapy. The delayed assessment should give much better insight into the likelihood of a durable clinical benefit for the patient. Demonstration that hypnotherapy has greater impact on functional MRI findings than pharmacotherapy would argue that resultant brain plasticity is related to mind-body therapy rather than due to altered sensory input (from the bladder).

## **10. Data Collection and Quality Assurance**

### **10.1 Data Collection Forms**

The Study Coordinator and her designee (neither of whom will perform data entry) will collect baseline information from subjects including Past medical history & Demographics sheet & baseline questionnaires (OAB-qSF, ISI, PBBC, PISQ-12, CRADI-8, IBS Module, BPIC, Expectation questionnaires administered) and 2, 6 and 12 month follow-up questionnaires and compliance information on CRFs. The questionnaires are standardized, validated questionnaires presented in their suggested paper formats. Unique patient identifiers are not included on the CRFs as the CRFs only include the research subject numbers, date and HRPO study # and CRF version numbers. The research staff responsible for data entry into the database will be blinded to subject randomization. The research nurse performing Cystometrics and fMRI tasks will not be involved in the fMRI interpretation. Drs. Mayer and Ketai, who will perform fMRI interpretation, will be blinded to subject randomization.

During this study all medical history, physical exam information, testing results and questionnaires obtained at baseline and follow-up will be for research purposes only and data will be kept in strict confidence and will be identified with a study code number unique to the subject without other patient identifiers. The database will be secured with password protection. The database will be built using the web-based platform, REDCap®, as recommended by the UNM CTSC. The study's data entry personnel will receive only coded information that is entered into the database under those identification numbers. Only coded information without unique patient identifiers will be entered into the study database. Only study personnel will have access to individually identifiable private information and data. Confidentiality will be maintained by keeping paper-based study subject folders for all enrolled subjects in a locked cabinet in the Urogynecology research area (this folder will include case report forms, laboratory reports, questionnaires, voiding diaries, intake forms). A separate log linking patient codes and unique patient identifiers will be kept on password protected computer available to study personnel.

## **10.2 Data Management**

Data will be collected on CRFs approved by the UNMH HRPO including demographic and patient history forms, eligibility forms, questionnaires, Cystometrics and fMRI task data sheets, pharmacotherapy side effect and hypnotherapy practice logs, treatment compliance logs as well as forms related to AE tracking. These data will be maintained as noted above by the Investigators and Research personnel. The database used by the UNM Urogynecology research team will be password protected. The database will be built using the web-based platform, REDCap®, as recommended by the UNM CTSC. The study's data entry personnel will receive only coded information that is entered into the database under those identification numbers. Only coded information without unique patient identifiers will be entered into the study database. Only study personnel will have access to individually identifiable private information and data. Confidentiality will be maintained by keeping paper-based study subject folders for all enrolled subjects in a locked cabinet in the Urogynecology research area (this folder will include case report forms, laboratory reports, questionnaires, voiding diaries, intake forms). Consents will be kept separate from these research folders and will be kept in a separate locked cabinet in the UNM Research Administrative area. A separate log linking patient codes and unique patient identifiers will be kept on password protected computer available only to study personnel. CRFs will include forms used to collect subject information including demographic, medical history forms, questionnaires, compliance forms, fMRI screening forms, inclusion and exclusion criteria forms as well as patient behavioral therapy instruction handouts.

Data collected at the Mind Research Network using standardized paper forms or digitally will only be identified with the study's unique identifier (ID) for the participant. The link between the name of the participant and the study ID will be kept confidential by the MRN on a secure portal. All data storage devices at the Mind Research Network are encrypted devices. Personally identifying information will not be stored in files on networked computers and paper forms. Such information will be kept in separate locked file cabinets. Electronic data are doubly protected against computer catastrophe. Data will be backed up daily. The backup system will be used only by a designated administrator, preventing accidental deletion even by project staff.

## **10.3 Quality Assurance**

### **10.3.1 Training**

Research Study Staff all complete training as required by the UNM (these include; Research University workshop for Human Research Protections Office submissions, Human Research Protections training certification, UNM Financial Conflicts of Interest training, UNM Health Sciences Center Culture of Compliance, UNM Health Sciences Center Code of Conduct and Compliance, HIPAA and Breach Notification, HIPAA Training, HIPAA and Accounting of Disclosure, Cash Management Trainings and Ethics training (Ethics: A Framework for Ethical Decision Making). In completing these training classes, research staff acknowledge the rules and regulations regarding human subjects protection, HIPAA regulations compliance, and all University-related policies and procedures governing research. These classes provide each coordinator with the tools to effectively and efficiently execute research protocols and maintain compliance with federal, state, and university regulations. In addition, the Research Information Specialist has completed the following training: Certified Clinical Research Coordinator (for certification), Essentials of Leadership', Patient Scheduling and the 2011 NIH Regional Grants Seminar. Each employee's training profile is reviewed annually with the Research Information Specialist to assure compliance with federal, state, and university guidelines.

Training for the medication counselor(s) will include 2-3 one hour training sessions, similar to the amount of training given in our hypnotherapy pilot study. Acceptability of counselor performance will be checked with the pharmacotherapy counseling fidelity checklist used by research staff to audit random sessions. Training for the hypnotherapists will include three 1-2 hour training sessions. Acceptability of hypnotherapist performance will be checked with the hypnotherapy fidelity checklist used by research staff to audit random sessions.

### **10.3.2 Quality Control Committee NA**

### **10.3.3 Metrics**

Outcome measures will have the following quality control metrics:

RCT outcomes:

1. Research study members who distribute and evaluate the voiding diary(s) will complete a training and certification process and random audits will be performed by research members one another's interpretations. See MOP "Voiding Diary Guidelines"



2. Research study members who distribute the treatment compliance and expectation questions will be trained and certified on their administration and interpretation and random audits will be performed by research members one another's interpretations.
3. The OAB-qSF<sup>15</sup>, ISI, the global questionnaire (PPBC),<sup>10,81</sup> PISQ-12<sup>64,65,66</sup>, CRADI-8<sup>87</sup>, IBS Module and BPIC questionnaire<sup>86</sup> are validated measures which will be administered in their recommended, standard format.

FMRI outcomes: BOLD-related evoked activity and functional connectivity maps will both undergo extensive QA procedure

1. The transformation matrix registering each subject's functional data to structural space will be visualized for accuracy (for both the evoked and resting state data)
2. Raw images will be examined for excessive motion as well as artifacts. In addition, the degree of motion will also be quantified for each individual based on the first two statistical moments from the cohort using previously published algorithms at the end of the study<sup>50</sup>
3. We will examine the fit of different modeling parameters on a per-subject basis.

#### **10.3.4 Protocol Deviations**

Data on adherence to the treatment protocol will be collected weekly during the treatment phase of the study by research staff and reviewed monthly by the PI. Data on adherence will be reviewed at each of the DSMB meetings (described above). Adherence of participants randomized to medications will be evaluated by performing review of the compliance to treatment forms collected at 2, 6 and 12 months for the pharmacotherapy group. Available data on the use of anti-cholinergics for urgency urinary incontinence suggests an overall non-compliance or withdrawal rate of 30% in randomized controlled trials and rates below 45% at 1 month and 13% at 1 year in clinical practice.<sup>54,21</sup> If average adherence falls below the suggested rate of 60%, a conference call will occur for study investigators to discuss methods for improving adherence without affecting the integrity of the study. However, given the data regarding anti-cholinergic side effects, it is quite possible that this non-adherence rate is not changeable. Protocol adherence in subjects randomized to hypnotherapy will be measured by monitoring compliance in keeping hypnotherapy appointments during the active intervention phase of the study, then review of compliance will be followed at 2, 6, and 12 months based on the compliance to hypnotherapy treatment forms. If adherence of hypnotherapy subjects falls below a suggested rate of less than 60% in the active treatment phase of the study, a conference call for study personnel to discuss methods for improving treatment adherence will occur.

A protocol deviation form will be completed by the study coordinator or her surrogate in her absence, for any event which occurs or is performed outside the study protocol. Protocol deviations include missed visits, incomplete visit assessments, informed consent-randomization deviations, errors in eligibility assessments, and study treatments. Treatment protocol deviations (e.g. off-protocol treatments) will be captured and documented on the Hypnotherapy Compliance and Pharmacotherapy Compliance forms that will be administered to subjects at their 2, 6 and 12 month follow-up. These will be reviewed by the Investigators (in the aggregate without individual identifiers to identify the frequency of occurrence) and will be reported to the DSMB at all their regularly scheduled meetings. Reporting of protocol deviations will follow UNM HRPO guidelines.

#### **10.3.5 Monitoring**

*Description of Plan for Data Quality and Management and Data Collection Forms*—The study staff under the over site of the PIs will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data verification will be performed by personnel other than the individual performing data entry onto the database on 10% of data collected. Data quality control metrics will be reviewed by the research team. The results of the data review will be incorporated into the reports for each DSMB meeting and in the Annual Report. The research team will be responsible for data collection and management for the project. Only the research team will have access to the data. Information will be collected by Investigators and research staff and recorded on the CRF's which will be considered source data. Data collection forms which have been developed prior to study initiation will be maintained as part of Good Clinical Practice (GCP). Research coordinator will review data collection forms for completeness. Data will be de-identified after the data is labeled with a participant code number. Study folders will be kept in a locked cabinet (see Database Protection above) only available to the study personnel. The study folders with data collection forms will be de-identified. Direct patient identifiers will be linked to the patient's code number log (or 'data link') kept separately from the study folders; the link is necessary in the event that the subject needs to be contacted in the future (see Database

Protection). Information with patient identifiers such as informed consent forms and HIPAA authorizations will be kept separate from the study folders in a secured area.

**Frequency of Data Review for this Study**— The frequency of data review for this study differs according to the type of data and is summarized in the following Table. The Reviewers will include the PIs, Study Coordinator and the Data Safety Monitoring Board.

<b>Data type</b>	<b>Frequency of review</b>	<b>Reviewer</b>
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	PI, Study Coordinator, DSMB
Status of all enrolled subjects, as of date of reporting	Quarterly	PI, Study Coordinator, DSMB
Adherence & Compliance data regarding study visits and interventions & Data Quality Review	Quarterly	PI, Study Coordinator, DSMB
AEs and rates	Per occurrence	PI, Study Coordinator, DSMB
SAEs	Per occurrence (see SAE reporting above)	PI, Study Coordinator, DSMB, NCCAM

## **11. Participant rights and Confidentiality**

### **11.1 Institutional Review Board (IRB) Review**

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the UNMH Human Research Protections Office (HRPO).

### **11.2 Informed Consent Forms**

Written informed consent will be obtained from each subject at study entry. Informed consent will be obtained by the following process:

- 1) Subjects will be asked if they are interested in study participation in a private setting, and if they verbalize interest, a copy of the consent forms will be explained and given to them to review so that they may discuss the study with family and friends.
- 2) The PI or Co-Is will meet with subjects to review the form and confirm the subject's understanding of the study and to answer their questions. Subjects will answer screening questions to ensure they are appropriate candidates for the study.
- 3) If subjects state that they are interested in study participation after explanation of the study as noted previously, an appointment will be made for subjects to return to sign the consent and fill out the baseline information and questionnaires.
- 4) If they state that they are not certain, they will be given the study coordinator's contact information so that they can call study personnel if they decide to participate in the study; a study appointment will be made for subjects to return to sign the consent after they contact study personnel.
- 5) At the enrollment appointment, which occurs in a private setting, subjects sign the consent after study personnel are certain that subjects have had appropriate counseling and understanding regarding the study and that the study and consent have been explained to them in a fashion congruent with their medical literacy. Consent will be obtained after screening is performed and will be re-reviewed in the future in the event changes are required. In general, consent will be obtained at the baseline visit. The PI or Co-Is, Study Coordinator(s) or Study Nurse(s) will obtain verbal and written informed consent on an IRB approved consent after explaining study and before collecting any data. Human subject's protection will follow local and national regulations at all times.

This study will not recruit Non-English speakers as the hypnotherapists are primarily English-speaking. Although we are not targeting vulnerable populations including students, Native American women or economically

disadvantaged women, we are drawing from the UNMH patient population which includes these groups of women. We will carefully proceed with informed consent. These subjects like all our subjects, will have protective measures taken to ensure that individuals understand the study and their roles as study subjects, and all subjects will be given appropriate time to decide whether or not they want to participate in the study. Subjects unable to give their own informed consent will not be enrolled in the study. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each study participant and this will be documented in the participant's record. In order to be comply with UNMHSC IRB regulations regarding potential future studies and analyses of findings and NIH directives regarding public access to NIH-funded databases, participants will be asked to sign an optional consent addendum for storage and use of data for future studies as this study has now completed enrollment. Data will be stored as outlined in section 10.2, and as stated in that section information in the database is de-identified with only research numbers used.

### **11.3 Participant Confidentiality**

The plan to ensure protection of subjects' privacy includes the following elements:

Subjects will be asked if they are interested in study participation in a private setting, and if they verbalize interest, they will be given a copy of the consent forms to read. If they choose to participate, arrangements will be made for subjects to sign the consent in the presence of a study investigator in a private setting. All subjects will be reassured that declining study participation will have no effect on the clinical care that they receive. Researchers will ask subjects' permission to review their medical records and record study findings (e.g. answers to the questionnaires, the standardized pelvic exam, cystometric results, voiding diary results, functional MRI results). No information will be given to anyone without the subject's permission; a Health Insurance Portability and Accountability Act (HIPAA) Authorization Consent will be obtained from the patient as required by the University of New Mexico IRB (HRPO). The investigators and the consents guarantee subject confidentiality, as required and substantiated in the University of New Mexico HRPO (IRB) study consents which further requires that all data will be identified with an identification code unique to the subject. During this study all evaluations, medical history and physical exams and questionnaires and imaging results performed at baseline and follow-up will be for research purposes only and data will be kept in strict confidence. All data, whether generated in the laboratory or on examinations will be identified with an identification code, a Participant ID (PID) otherwise referred to as a study number, unique to the subject. All records will be kept in a locked file cabinet. Information will not be released without written permission of the participant, except as necessary for monitoring by the UNM HRPO or NCCAM. (Please also refer as well to the above sections; section 10.1 Data Collection forms and 10.2 Data Management).

### **11.4 Study Discontinuation**

The study may be discontinued at any time by the UNM HRPO (IRB), the NCCAM or other government agencies as part of their duties to ensure that research participants are protected.

## **12. Committees**

Data Safety Monitoring Board (see section 7.6 and DSMP)

## **13. Publication of Research Findings**

Publications of the results of this study will be determined by the PIs and Co-Is of this study. Authorship will follow the guidelines of the International Committee of Medical Journal Editors and require authorship credit based on 1) substantial contributions to conception and design and acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors will meet condition 1, 2, and 3.

Final research data will be shared via abstract submission, presentation at appropriate research meetings and publications in peer reviewed journals. Manuscripts arising from this funding will be submitted to PubMed Central upon acceptance for publications. Our project will register at Clinical trials.gov and the project design will be publically available. Any presentation, abstract or manuscript will be made available for review by NCCAM if desired prior to submission.

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