Draft Guidance for Industry and FDA Staff

Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Urology and Lithotripsy Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices
Office of Device Evaluation

Preface

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Draft Guidance for Industry and FDA Staff

Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This draft guidance document describes FDA's proposed recommendations for clinical investigations of medical devices indicated for the treatment of urinary incontinence. Urinary incontinence is defined as the involuntary loss of urine. It is a common health problem, especially among women. Depending on the definition of urinary incontinence used, the prevalence ranges from 3% to 55% of the U.S. population.[1] The prevalence of urinary incontinence also increases with advancing age,[2] implying that the impact of this condition is likely to increase over the next several decades as the U.S. population ages. Urinary incontinence is associated with poor self-rated health and quality of life, social isolation, and depressive symptoms,[3] and is a significant medical condition with considerable public health impact.

The ultimate goal when investigating a urinary incontinence device is to design a study using objective, unbiased outcomes to measure the safety and effectiveness of the device. Conducting objective clinical studies to investigate the safety and effectiveness of urinary incontinence devices, however, is fraught with difficulties due to unique challenges posed by this condition and patient population. Major challenges faced when designing a clinical study to assess the safety and effectiveness of a urinary incontinence device include the inherent variability and subjectivity of the typical outcome measures commonly used to assess the device effectiveness, the significant

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[1] Center for Disease Control, "Urologic Diseases in America", pp. 71-152, 13 September 2005, http://www.cdc.gov/std/research/2004/Urologic_Diseases_in_America.pdf.

[2] JA Fantl, DK Newman, J Colling, et al. Urinary incontinence in adults: acute and chronic management. Clinical Practice Guideline Number 2 (1996 Update). Rockville, MD: Agency for Health Care Policy and Research, 1996, AHCPR Publication No. 97-0682.

[3] JL Melville, K Delaney, K Newton, W Katon. Incontinence Severity and Major Depression in Incontinent Women. *Obstet Gynecol*, 2005, 106(3):585-592.

placebo effect associated with some of these outcome measures, and the heterogeneous nature of the general patient population. These challenges are described in further detail, below.

The psycho-social dimension of urinary incontinence inherently relies on the patients' perceptions of their condition, and quality of life is the primary motivator of patients to seek treatment for their condition. While quality of life is an important outcome measure, it is subjective and inherently difficult to measure reliably, and may be age- and symptom-dependent.[4]

There is a strong behavioral component to urinary incontinence, and enrollment in a clinical study in and of itself may make subjects more aware of their voiding habits and potential risk factors. This phenomenon makes urinary incontinence studies susceptible to a significant placebo effect.[5,6]

Patients' activities of daily living (e.g., mobility, recreation, exercise) and daily habits (e.g., diet, fluid intake) are difficult to control, yet can directly affect the frequency and amount of urine loss. Thus, variability in the types and levels of activities among patients seeking treatment for urinary incontinence is an important issue.

There can be a high degree of heterogeneity in the potential patient population, which could introduce bias if covariates are not carefully balanced between treatment and control arms.

For these reasons, we believe sound clinical study design is essential when investigating the safety and effectiveness of a device for urinary incontinence. We believe that, in general, a randomized, controlled trial is the least burdensome means of collecting data to demonstrate safety and effectiveness of urinary incontinence devices. Reasons supporting this view are that the randomized controlled trial inherently balances patient covariates between study groups, permits assessment of placebo effects, and may provide the most reliable method of assessing subjective or variable safety and effectiveness outcome measures. In considering alternative study designs, using patients as their own control or using a historical control may hinder the ability to demonstrate safety and effectiveness in most investigations. Statistical concerns underlying this recommendation include both general considerations, such as regression to the mean, and the disease-specific considerations listed above. These and other study design recommendations are discussed in detail in section **5. Pivotal Study Recommendations**.

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[4] S. Hunskaar, A. Vinsnes. The quality of life in women with incontinence as measured by Sickness Impact Profile. *J Am Geriatr Soc*, 1991, 39(4):378-382.

[5] I. Yalcin, R.C. Bump,. The effect of previous treatment experience and incontinence severity on the placebo response of stress urinary incontinence, *Am J Obstet Gynecol*, 2004, 191:194-197.

[6] J.H. Schagen van Leeuwen, R. Castro, M. Busse B.L. Bemelmans. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms, *Eur Urol*, 2006, 50(3):440-452.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to clinical trials of urinary incontinence devices and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2. Scope

This draft guidance document addresses the general clinical study design concepts that you should consider when designing clinical investigations of medical devices indicated for the treatment of urinary incontinence. This document does not address preclinical testing issues, which should, on a case-by-case basis, take into account the specific clinical indications and technology of the device.

Premarket notifications (510(k)s) for class II devices, as well as class I devices with new indications or technology that exceed the limitations of exemption, may sometimes include clinical data that support the performance specifications of the device. In accordance with the Federal Food, Drug, and Cosmetic Act (the Act), the agency will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new class I and II urinary incontinence devices, unless there is a need for clinical information to support a determination of substantial equivalence. (See sec. 513(i)(1) of the Act (21 U.S.C. 360(i)(1)). While, in general, clinical studies may not be needed for most class I and II urinary incontinence devices, FDA may recommend that you collect clinical data for class I and II urinary incontinence device with any one of the following:

- indications for use dissimilar from a legally marketed device of the same type;
- designs dissimilar from designs previously cleared under a premarket notification; or
- new technology, i.e., technology different from that used in legally marketed devices of the same type.

FDA will consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.

Premarket approval applications (PMAs) for class III devices require valid scientific evidence in the form of clinical data to demonstrate a reasonable assurance of safety and effectiveness (21 CFR 860.7).

This document is intended to cover any type of urinary incontinence device undergoing clinical investigation to support a marketing submission or application. The device technologies may include, but are not limited to, the device types shown in the tables below.

The following table lists class III (premarket approval) urinary incontinence devices.

Classification (21 CFR)	**Class**	**Product Code**	**Description**
GASTROENTEROLOGY-UROLOGY DEVICES			
876.5270 Implanted electrical urinary continence device	III	EZT	Pacemaker, bladder
	III	EZW	Stimulator, electrical, implantable, for incontinence
876.5280 Implanted mechanical/hydraulic urinary continence device	III	EZY	Device, incontinence, mechanical/hydraulic
†	III	LNM	Agent, bulking, injectable for gastro-urology use
†	III	OCK	Transurethral occlusion insert, urinary incontinence-control, female

†Requires premarket approval application before marketing (see section 513(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(a))).

The following table lists class I and II urinary incontinence devices.

Classification (21 CFR)	Class	Product Code	Description
GASTROENTEROLOGY-UROLOGY DEVICES			
876.5160 Urological clamp for males	I 510(k) Exempt	FHA	Clamp, penile
876.5310 Nonimplanted, peripheral electrical continence device	II	NAM	Stimulator, peripheral nerve, non-implanted, for pelvic floor dysfunction
876.5320 Nonimplanted electrical continence device	II	KPI	Stimulator, electrical, non-implanted, for incontinence
876.5920 Protective garment for incontinence	I 510(k) Exempt	EYQ	Garment, protective, for incontinence
N/A	Unclassified	MNG	External urethral occluder, urinary incontinence-control, female
GENERAL AND PLASTIC SURGERY DEVICES			
878.3300 Surgical mesh	II	FTM	Mesh, surgical
	II	FTL	Mesh, surgical, polymeric
878.4400 Electrosurgical cutting and coagulation device and accessories	II	MUK	Electrosurgical radiofrequency system, stress urinary incontinence, female
	II	NVJ	Applicator, transurethral, radio frequency, for stress urinary incontinence in women
OBSTETRICAL AND GYNECOLOGICAL DEVICES			
884.1425 Perineometer	II	HIR	Perineometer
884.1720 Gynecologic laparoscope and accessories	II	OCQ	Laproscopic bladder-neck suspension instrument, stress urinary incontinence
884.3575 Vaginal pessary	II	HHW	Pessary, vaginal

If a clinical study is needed to support PMA approval or 510(k) clearance, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. Most of the devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m).[7] In addition to the requirement of having a FDA-approved IDE, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).[8]

3. Clinical Indications

The condition of urinary incontinence can be divided into several categories, depending upon the physiologic mechanism triggering urine loss.[9] These categories are listed and defined below.

Stress Incontinence is urinary incontinence during physical activities that increase intra-abdominal pressure, such as coughing, sneezing, or lifting. It occurs whenever the intra-abdominal pressure exerted on the bladder exceeds the closing pressure of the bladder neck. Stress incontinence can be further divided into two subcategories, hypermobility and intrinsic sphincter deficiency, which are defined below.

Hypermobility is stress incontinence caused by the abnormal descent of the bladder neck below the zone of abdominal pressure. When intra-abdominal pressure rises, pressure to the bladder increases but the zone of pressure does not include the bladder neck.

Intrinsic Sphincter Deficiency (ISD) is stress incontinence caused by weakness of the urinary sphincter.

Note: Hypermobility and ISD are not mutually exclusive. In cases where the two subcategories of stress incontinence co-exist, the patient's diagnosis is typically based on the predominant mechanism of urine loss. As detailed later under section **I. Patient Selection Criteria**, your study should properly define and document the criteria for study entry to verify that subjects with co-existing categories of incontinence are appropriate candidates for the investigational treatment and will not confound the study's conclusions.

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[7] See Significant Risk and Nonsignificant Risk Medical Device Studies, http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

[8] For devices that are not significant risk, sponsors of clinical investigations still must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

[9] G.D. Webster, M.L.Guralnick,. in Campbell's Urology, edited by PC Walsh, AB Retik, V.E. Darracott Jr., , et al., Philadelphia: Saunders, 2002, 8th edition, vol. 2, pp. 901.

Urge Incontinence is urinary incontinence secondary to a sudden, strong desire to void (urgency). This type of incontinence is generally caused by either an involuntary detrusor contraction or neurological impairment.

Mixed Incontinence is a combination of stress and urge incontinence.

Overflow Incontinence is urinary incontinence where the leakage of urine is due to the urine volume exceeding the normal capacity of the bladder. This type of incontinence occurs secondary to poor bladder emptying caused by either impaired detrusor contractility or outflow obstruction.

Functional Incontinence is urinary incontinence that occurs when physical or mental disabilities prevent a person from getting to a bathroom before they urinate. Disabilities that often lead to functional incontinence are problems with walking and dementia.

Continuous Incontinence is urinary incontinence where the leakage of urine is due to either a urinary tract fistula or ectopic ureter that allows urine to bypass the urethral sphincter.

A wide range of underlying mechanisms may cause or contribute to urinary incontinence, and patients' outcomes after device therapy generally depend on the underlying physiological mechanism of urine loss. Therefore, we recommend you tailor the indication of your device to the specific categories of urinary incontinence relevant to the device's mechanism of action and targeted for treatment in your study.

4. Pilot Study Recommendations

We recommend you separate your urinary incontinence device investigation into phases to minimize the risks to investigational subjects and to gain clinical experience in using your device prior to initiating a large-scale clinical study. These phases typically involve an initial study, commonly referred to as a "pilot" or "feasibility" study, followed by a pivotal study.

During the pilot study phase, you can gain valuable information regarding short-term safety, treatment technique, study conduct, and the optimal patient population. Additionally, information obtained from exploratory analyses of the pilot study results may be used to refine the pivotal study hypothesis, identify the most suitable endpoints and estimate their response to treatment and variance, and investigate potential indications for use. Information from a pilot study may also allow a limited evaluation of the factors that may introduce bias (e.g., covariates).

A pilot study generally involves a limited number of subjects and sites, and close monitoring of all adverse events. The size and duration of the pilot study can vary depending upon the type of device being investigated. For example, a pilot study for a novel or high-risk device generally begins with a smaller sample size and follows subjects for a longer period of time. We recommend that the pilot study protocol prospectively define the minimum dataset (i.e., number of enrolled subjects and the minimum duration of follow-up on those subjects) that

will be collected to support initiating the pivotal study. For investigations conducted under an IDE application, we recommend you submit a complete report of the pre-specified pilot study dataset prior to or at the time of the request for pivotal study approval. Analysis of the pilot study dataset will help determine whether it is appropriate to initiate the pivotal study.

We recommend you randomize subjects in your pilot study between study groups to estimate the effectiveness of both the investigational device and the control. This information can help you adequately power the subsequent pivotal study. We believe it is unlikely that the pilot study data can be pooled with pivotal study data, since there are often differences in the pilot and pivotal study protocols. If you intend to pool pilot and pivotal study results, we recommend you provide a rationale showing that it is statistically and clinically valid to pool the data from the pilot and the pivotal studies.

5. Pivotal Study Recommendations

The purpose of the pivotal clinical study is to collect the primary evidence of safety and effectiveness data to support a marketing submission or application. Proper pivotal study design can minimize error and bias, and facilitate an objective assessment of the investigational device. We recommend you conduct a pivotal study of a urinary incontinence device at multiple clinical sites to assess the consistency of the study results among a wide variety of investigators and patients, and to increase the chance that the study population is representative of the general patient population.

Your study design should address the factors described below.

A. Study Objective

The study objective forms the basic framework for the study design and helps in identifying the control, the primary endpoint, the study follow-up duration, and the primary statistical analysis. The statistical hypothesis follows directly from the primary objective of the study. For these reasons, you should state a clear study objective before you design your pivotal clinical trial. All elements of your trial design should be consistent with your study objective.

B. Minimizing Bias

One consideration in the design of any clinical study is how to minimize known or suspected sources of bias so the study conclusions can be clearly and objectively assessed. Bias occurs when any characteristic of the investigator, study population, or study conduct interferes in a systemic way with the ability to measure a variable accurately. **Appendix 1** identifies common sources of potential bias and methods that are frequently employed to mitigate them. These sources of bias are discussed individually in the **C. Randomization and Control**, **D. Blinding**, **I. Patient Selection Criteria**, and **N. Statistical Analysis Recommendations** sections of this guidance document.

If sources of bias are not adequately minimized, the validity of the study's conclusions may be questionable. For all study designs, we recommend your protocol include a section describing how the study design intends to minimize bias.

C. Randomization and Control

Clinical investigations of urinary incontinence devices pose unique challenges, such as the influence of subjects' perceptions on outcome (placebo effect), the inherent variability and subjectivity of the available effectiveness endpoints, and heterogeneity within the patient population. For most urinary incontinence devices, we believe that these challenges are most efficiently overcome by using randomized, controlled trial designs. The benefit of a randomized, controlled trial is its tendency to balance confounding factors between study groups and minimize the potential for bias.

The potential advantages of conducting a randomized, controlled trial extend not only to the evaluation of device effectiveness, but also to the evaluation of safety. Adverse event rates may be affected by factors such as subject characteristics, device design, evolving procedural methods, and operator experience, and are often much more difficult to evaluate when using historical control data.

Randomizing subjects between study groups is a standard method for minimizing selection bias and controlling for confounding factors. Selection bias occurs when subjects possessing one or more important prognostic factors appear more frequently in one study group than the other. The randomization process assigns subjects to an intervention or control group such that each subject has a prospectively defined chance of being selected for each group. Randomization also protects the trial from conscious or subconscious actions on the part of the study investigators that could lead to study groups that are not comparable, e.g., selecting the most incontinent patients for the therapy thought by the study investigator to be the more aggressive treatment. We recommend you prospectively define the randomization method in your study protocol. The randomization method should balance the assignment of subjects within each site (e.g., by block randomization), preclude investigators and other study personnel from predicting or influencing the assignment of subjects, and prevent natural patterns of patient behavior from influencing study assignment.

When designing a randomized, controlled study, we recommend you select an appropriate control therapy. There are a variety of scientific and ethical issues that may influence the choice of control.[10] Typically, the current standard of care for the targeted patient population represents the most clinically meaningful control. However, other factors may also influence this decision. We recommend that you address each of the following factors when choosing a control:

- standard of care;

[10] R. Temple, S.S. Ellenberg. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Ann Intern Med*, 2000, 133(6):455-461.

- desired indications for use of the investigational device;
- patient population being targeted;
- risks versus benefits (i.e., to permit a clinically meaningful comparison, it is desirable for the risk-to-benefit ratio of the control treatment to be comparable to that of the investigational device);
- ability to effectively blind the subject and evaluator;
- time to treatment effect; and
- device design.

Potential control therapies include:

- use of an accepted surgical procedure;
- treatment with an legally marketed medical device;
- treatment with an approved drug;
- behavioral therapy; and
- sham treatment.

A control that consists of treatment with a legally marketed urinary incontinence device that is similar in design to the investigational device is often a desirable option because study design, subject enrollment, and data analysis may be straightforward. For example, it might be both simple and appropriate to use a randomized study to compare the safety and effectiveness of an investigational injectable bulking agent to those of a legally marketed injectable bulking agent.

Sham controlled studies represent one study design and choice of control group which may allow for discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors such as patient or observer expectations. This type of study design may be most appropriate for studies with subjective endpoints, such as reduction in patient-reported symptoms. Sham surgical procedures/treatments typically involve more risk than the placebo control arm in drug trials and should be used in limited circumstances. This study design should only be considered when it is methodologically necessary, i.e., when designs that are unblended are methodologically unacceptable (e.g., because endpoints are subjective) and when a "no treatment" control is methodologically required. Furthermore, the withholding of treatment should not lead to serious harm, such as death or irreversible morbidity. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that investigators, institutional review boards, and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully considered and planned. Additionally, if a sham procedure/treatment is being considered in a clinical investigation involving children, the requirements of 21 CFR Part 50 Subpart D also apply.

You can employ several strategies to facilitate patient recruitment and retention in concurrently controlled studies, such as through randomization ratios other than 1:1 and

crossover study designs that would allow either sham or medically managed control patients to receive treatment with the investigational device and after a pre-specified time offer potential subjects increased availability to the investigational treatment.

Generally, we recommend a randomized, controlled trial to address the challenges described in this guidance document. However, if you use an alternative study design, we recommend that you show that it is scientifically sound and addresses the relevant safety and effectiveness questions. While we recognize that there is no unique "best design" for urinary incontinence investigations, we consider the elements discussed in this document as core features of well-designed studies. As noted, we will consider alternative study designs, but we recommend that you clearly explain the scientific arguments supporting the use of your alternative design (e.g., How will bias be minimized? How does the study address placebo effects? How does the control compare with current patient characteristics and standards of clinical care?).

For all study designs, we recommend that you collect detailed baseline and demographic information on all study subjects so that the study groups can be assessed for imbalances in prognostic factors.

D. Blinding

Sources of bias in a clinical trial include investigator bias, evaluator bias, and placebo or sham effect (defined in **Appendix 1**). To protect the study against these sources of bias, we recommend you incorporate blinding into your study design. Single-blind designs mask the subject from knowing what intervention was assigned. Double-blind studies mask both the subject and the investigator. In cases where single- and double-blind designs are not feasible, it is usually possible to use a blinded third-party evaluator for the evaluation of certain outcome measures (e.g., pad weight testing, evaluation of voiding diary information, quality of life, cystoscopy, adverse events).

Blinding is usually accomplished by coding the interventions and having an individual who is not a member of the patient care team control the key to the code. Since bias introduced by breaches in blinding can be very difficult to assess in the analysis, we recommend that you do not break the code until the analysis is complete.

If study subjects and investigators (or other evaluators) are going to be blinded to the subject's treatment allocation (i.e., investigational devices vs. control therapy), your protocol should collect information to assess the effectiveness of the blinding (e.g., by asking subjects which study group they think they are in). Your protocol should also describe the blinding methodology and specify when blinding will be broken.

E. Study Endpoints

Your clinical protocol should clearly specify and support the study's primary and secondary endpoints. To ensure the collection of meaningful results, these endpoints should be clinically relevant to the specific condition and patient population you intend to target in the study.

Listed below are additional factors to consider when selecting the optimum endpoints for clinical investigations of urinary incontinence devices.

1. Primary Endpoints

The primary safety and effectiveness endpoints should be the clinical measures that best characterize the safety and effectiveness of the device and used to judge the overall success of the study. For a urinary incontinence device study, the primary endpoint specified in the statistical hypothesis is usually an effectiveness endpoint, which, in turn, directly affects the indications for use.

2. Primary Effectiveness Endpoint

The selection of the primary effectiveness endpoint can be one of the major challenges in designing an investigation of a urinary incontinence device. The primary effectiveness endpoint should be clinically meaningful, and, ideally, should fully characterize the effect of treatment. However, due of the nature of urinary incontinence, it is difficult to find an effectiveness measure that is objective and repeatable (i.e., has low test-retest variability), yet is also meaningful to patients and relevant to their reasons for seeking treatment. For this reason, defining the "optimum" primary effectiveness endpoint can be a challenge.

The following table lists commonly used effectiveness endpoints for urinary incontinence therapies, along with their potential advantages and disadvantages.

Endpoint	Potential Advantages	Potential Disadvantages
1-Hour Pad Weight Test (Amount of urine leakage experienced by the subject in 1 hour during a standardized series of activities or exercises in the investigator's office)[11]	• Objective • Standardized • Assesses severity of urine leakage	• Outcomes other than dryness may not be meaningful to patients • Not correlated with patients' daily activities • Poor to moderate sensitivity[12] • Subject to variability
24-Hour Pad Weight Test (Amount of urine leakage	• Objective • Correlated with patients' daily activities	• Outcomes other than dryness may not be meaningful to patients • Less standardized

[11] P. Abrams, J.G. Balivas, S.L. Stanton, J.T. Anderson. The standardization of terminology of lower urinary tract function. *Scand J Urol Nephrol Suppl*, 1988, 114:5-19.

[12] A. Tubaro, W. Artibani, C. Bartram, et al., "Imaging and other investigations," in Incontinence: Basics and Evaluation, edited by P. Abrams, L. Cardozo, S. Khoury, and A. Wein A., vol. 1, Paris: Health Publication Ltd., 2005, pp. 775.

Endpoint	Potential Advantages	Potential Disadvantages
experienced by the subject at home during a 24-hour period; all pads used during the test period are weighed before and after use)[13]	• High sensitivity[14] • Assesses severity of urine leakage	• Subject to variability • Requires patient compliance
Number of Incontinence Episodes/Day (Obtained using a voiding diary)	• Objective • Meaningful to patients • Correlated with patients' daily activities	• May not directly correlate with the severity of urine leakage • Less standardized • Subject to variability • Requires patient compliance
Number of Pads Used/Day (Obtained using a voiding diary)	• Objective • Meaningful to patients • Correlated with patients' daily activities	• May not directly correlate with the severity of urine leakage • Less standardized • Subject to variability • Requires patient compliance
Quality of Life (Assessed using a validated questionnaire)	• Meaningful to patients[15] • Standardized • Patient's daily activities taken into account	• Significant placebo effect[16] • Subjective • Subject to variability • Not correlated with the severity of urine leakage
Urodynamics Measure (Measurement such as leak	• Objective • Standardized • Less subject to variability	• Not meaningful to patients • Not correlated with patients' daily activities

[13] L. Jørgensen, G. Lose, P. Thunedborg. Diagnosis of mild stress incontinence in females: 24-hour home pad weight testing versus the 1-hour ward test. *Neurourol Urodyn*, 1987, 6:165-166.
[14] A. Tubaro, W. Artibani, C. Bartram, et al., "Imaging and other investigations," in Incontinence: Basics and Evaluation, edited by P. Abrams, L. Cardozo, S. Khoury, and A. Wein., vol. 1, Paris: Health Publication Ltd., 2005, pp. 777.
[15] K.S. Kinchen, K. Brugio, A.C. Diokno, N.H. Fultz, et al., Factors associated with women's decisions to seek treatment for urinary incontinence. *J Women's Health (Larchmt)*, 2003, 12(7):687–698.
[16] J.H. Schagen van Leeuwen, R. Castro, M, Busse, B.L. Bemelmans. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms, *Eur Urol*, 2006, 50(3):440-452.

Endpoint	Potential Advantages	Potential Disadvantages
point pressure, cystometric outcome, etc.)		• Invasive; patients may be unwilling to comply • Specific to particular categories of incontinence

In light of these potential advantages and disadvantages, we recommend that a urinary incontinence device investigation use one or both of the following measures as the primary effectiveness endpoint. Our recommendation is derived from a detailed comparison of the relative benefits and limitations of the various endpoints, which is consistent with a consensus effort sponsored by the World Health Organization.[17]

Reduction in urine leakage, as assessed by pad weight, at the follow-up visit (relative to baseline)

The most meaningful measure of success for any urinary incontinence treatment is dryness, which is the outcome that patients ultimately seek. Therefore, your protocol should prospectively define dryness with respect to pad weight as pad weight increase during the test of less than X grams (where the variable X denotes a negligible increase in weight due to measurement uncertainty, subject perspiration, or other source). For the 1-hour pad weight test, we recommend defining dryness as pad weight increase of less than 1 gram.[18] For the 24-hour pad weight test, we recommend defining dryness as pad weight increase of less than 1.3 grams.[19]

Although dryness is the ultimate goal of treatment, we recognize that many patients are satisfied if they only experience a reduction in urine leakage. Based on our experience reviewing urinary incontinence studies, we recommend defining the clinically meaningful level of improvement in pad weight as greater than 50% reduction from baseline.

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[17] C. Payne, P. Van Kerrebroeck, J. Blaivas, et al., "Research Methodology in Urinary Incontinence" in Incontinence, edited by Abrams P, Cardozo L, Khoury S, and Wein A, Paris: Health Publication Ltd., 2002, pp.1058–1061.

[18] A. Tubaro, W. Artibani, C. Bartram, et al., "Imaging and other investigations," in Incontinence: Basics and Evaluation, edited by P. Abrams, L. Cardozo, S. Khoury, and A. Wein A., vol. 1, Paris: Health Publication Ltd., 2005, pp. 779.

[19] A. Tubaro, W. Artibani, C. Bartram, et al., "Imaging and other investigations," in Incontinence: Basics and Evaluation, edited by P. Abrams, L. Cardozo, S. Khoury, and A. Wein A, vol. 1, Paris: Health Publication Ltd., 2005, pp. 779.

To combine the strengths of the 1-hour pad weight test (i.e., highly standardized) and the 24-hour pad weight test (i.e., correlated with patients' daily activities, high sensitivity), we recommend that you incorporate both pad weight tests in a composite primary effectiveness endpoint. A composite endpoint incorporates two or more effectiveness endpoints into a single, unified endpoint using a clearly stated decision rule, for example:

- reduction in pad weight and reduction in number of incontinence episodes; or
- reduction in pad weight and improvement in quality of life.

Reduction in the number of incontinence episodes per day at the follow-up visit (relative to baseline)

We recommend that investigators assess this endpoint using a standardized voiding diary that documents the daily chronological record of fluid intake, incontinence episodes with associated activity and perceived level of urgency, severity of each incontinence episode (i.e., estimated volume of leakage), pad usage, and normal voiding episodes with measured volume. To reduce within-patient variability, we recommend collecting this voiding diary information over 3 consecutive days and reporting the average number of incontinence episodes per day.

We recommend your protocol define dryness with respect to number of incontinence episodes as zero (0) episodes per day. Additionally, we recommend your protocol specify the clinically meaningful level of improvement in the number of incontinence episodes per day as greater than 50% reduction from baseline.

If you select only one of these outcome measures, reduction in pad weight or reduction in number of incontinence episodes, as the primary effectiveness endpoint, we recommend your protocol include the other as a secondary endpoint.

Alternatively, a composite endpoint in the primary assessment of effectiveness can overcome the disadvantages of using a single measure as the primary effectiveness endpoint for a urinary incontinence device study.

3. Primary Safety Endpoint

We generally recommend you base the primary safety endpoint on the incidence and severity of adverse events. However, if your device is associated with, or intended to mitigate, a specific safety concern, then it may be appropriate to base the primary safety endpoint on the specific adverse events associated with that concern, while still recording all adverse events.

To collect safety information reliably, we recommend your protocol instruct investigators to record all adverse events, regardless of whether you believe they are device-related or anticipated. Events you should routinely record include, but are not limited to:

- genitourinary events (i.e., events associated with the urinary tract or the surrounding genital region);
- infections;
- pain and discomfort;
- foreign body reactions;
- secondary or unplanned surgical interventions;
- all transient post-procedure events; and
- deaths.

Investigators should categorize adverse events according to their respective relatedness to the device or procedure, and rate their severity. Additionally, we recommend that investigators document the onset and resolution times of each adverse event, noting the method of resolution. Because of the difficulty determining the root cause of genitourinary events, we recommend you categorize all genitourinary events conservatively as either device- or procedure-related.

We recommend that the safety analysis include a descriptive assessment of the types and frequency of adverse events observed in the study, with comparison to the control therapy, as appropriate.

4. Secondary Endpoints

FDA believes secondary endpoint measures, by themselves, are not sufficient to characterize fully the treatment benefit. However, these measures may provide additional characterization of the treatment effect.[20] Specifically, secondary endpoints can:

- supply background and understanding of the primary endpoints, in terms of overall direction and strength of the treatment effect;
- be the individual components of a composite primary endpoint, if used;
- include variables for which the study is underpowered to definitively assess;
- aid in the understanding of the treatment's mechanism of action;
- be associated with relevant sub-hypotheses (separate from the major objective of the treatment); or
- be used to perform exploratory analyses.

Assuming that the primary safety and effectiveness endpoints of the study are successfully met, we recommend you analyze the secondary endpoints to provide supportive evidence concerning the safety and effectiveness of the device, as well as to support descriptions of device performance in the labeling. To minimize bias, your protocol should prospectively

[20] R.B. D'Agostino, Sr., Controlling alpha in a clinical trial: the case for secondary endpoints. *Statist Med*, 2000, 19(6):763-766.

identify all secondary endpoints, indicating how the data will be analyzed and what success criteria will be applied.

Although there are many possible secondary endpoints to consider for clinical investigations of urinary incontinence devices, we recommend your protocol include the endpoints discussed below.

Quality of Life

Urinary incontinence is strongly associated with impairment of quality of life, which typically leads patients to seek treatment.[21] Therefore, we recommend your protocol instruct investigators to assess the quality of life of study subjects using a validated measure specific to urinary incontinence.[22] For example, the Incontinence Quality of Life (I-QOL) questionnaire is an instrument for which validity, reliability, and responsiveness have been demonstrated.[23,24] To analyze improvement in quality of life, we recommend your protocol specify a clinically meaningful difference. For instance, a 2.5-point change in the I-QOL has been determined to be the minimum clinically meaningful difference for women with stress urinary incontinence.[25]

Sexual Function

Given the proximity of urinary incontinence devices to the genitalia, we recommend your protocol assess the impact of the device upon sexual function using a validated, gender-specific measure of sexual function.

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[21] K.S. Kinchen, K. Brugio, A.C. Diokno, N.H. Fultz, et al., Factors associated with women's decisions to seek treatment for urinary incontinence. *J Women's Health (Larchmt)*, 2003, 12(7):687-698.

[22] There are numerous incontinence-specific quality of life measures. These measures differ in the populations and settings in which they were developed and validated, and in their potential applicability to other patient groups. The 3rd International Consultation on Incontinence discusses many of these measures and states current international consensus on incontinence-specific quality of life questionnaires. [J. Donovon, R. Bosch, M. Gotoh, S. Jackson, et al., "Symptom and quality of life assessment" in Incontinence: Basics and Evaluation, edited by P. Abrams, L. Cardozo, S. Khoury, and A. Wein, vol. 1, Paris: Health Publication Ltd., 2005.]

[23] T.H. Wagner, D.L. Patrick, T.G. Bavendum, M.L. Martin, et al., Quality of life of persons with urinary incontinence: development of a new measure. *Urology*, 1996, 47(1):67-72.

[24] D.L. Patrick, M.L. Martin, D.M. Bushnell, I. Yalcin, et al., Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). *Urology*, 1997, 53(1):71-76.

[25] I. Yalcin, D.L. Patrick , K. Summers, K. Kinchen, et al. Minimal clinically important differences in incontinence quality-of-life scores in stress urinary incontinence, *Urology*, 2006, 67(6):1304-1308.

Leak Point Pressure

We recommend your protocol specify this urodynamic parameter as a secondary endpoint when the device is indicated for the treatment of stress urinary incontinence secondary to intrinsic sphincter deficiency (ISD), or when the device has the potential to negatively affect the anatomy surrounding the external urinary sphincter.

Post-void Residual (PVR) Urine Volume

We recommend your protocol include PVR as a secondary endpoint if the device has the potential to impact bladder emptying.

Patient Satisfaction

We recommend your protocol include a standardized patient satisfaction survey as a secondary endpoint to rate subject satisfaction with each aspect and dimension of treatment (e.g., rating of improvement, discomfort, ease of use, confidence in social situations, confidence in active situations, overall satisfaction).

Recommendations regarding the statistical analysis of secondary endpoints are discussed below in **N. Statistical Analysis Recommendations**.

F. Study Duration

You should design your study to assess whether the treatment effect of your urinary incontinence device, as measured using the primary and secondary effectiveness endpoints, persists for a clinically meaningful period of time. Additionally, longer follow-up duration may diminish placebo effects.[26] For urinary incontinence devices that are intended either as a curative treatment or for long-term management, we recommend your study follow subjects during the premarket follow-up period for 1 year following treatment to document the stability of the treatment effect. It is possible, however, that longer term follow-up may be appropriate, depending upon a variety of device-specific factors. Examples of such factors include, but are not limited to, unique device material properties, retreatment or repeated use requirements, and delay in the time to achieve the full treatment effect. In studies where device retreatment is permitted, we recommend the follow-up duration refer to the period following final treatment.

In addition to the premarket follow-up considerations discussed above, long-term postapproval studies may be appropriate for class III (premarket approval) devices to assess the stability of the treatment effect and any specific long-term safety and effectiveness concerns that arise during the premarket study. For devices for which postapproval studies are anticipated or possible, we recommend your study continue to follow subjects annually beyond marketing approval or clearance. In the event that FDA requires a postapproval study

[26] J.H. Schagen van Leeuwen, R. Castro, M. Busse, B.L. Bemelmans. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms, *Eur Urol*, 2006, 50(3):440-452.

as a condition of the PMA approval,[27] incorporating this extended follow-up in the original pivotal study will allow you to convert the premarket study into a postapproval study, avoiding the problems of obtaining new informed consent from study subjects for additional follow-up and recruiting new subjects.

G. Statistical Hypothesis

The statistical hypothesis follows directly from the primary objective of the study and establishes the framework for the design of your study. The statistical hypothesis is also used to calculate the sample size and helps determine the statistical methodology that will be used to analyze the primary study endpoint. For these reasons, you should formulate a clear statistical hypothesis that is consistent with the primary objective of your study when you design your pivotal clinical trial. All other elements of your clinical study design should be consistent with your statistical hypothesis.

For non-inferiority studies, we recommend the hypothesis incorporate a non-inferiority delta level that reflects a maximum tolerable difference that is "clinically insignificant" (i.e., "not clinically meaningful") in the analysis of the primary endpoint. Larger values of the non-inferiority delta level are usually supported by demonstrating significant benefits in the safety of the investigational device. For superiority studies, we recommend the hypothesis state a clinically meaningful level of improvement (i.e., a superiority delta) by which the investigational device should exceed the control with regard to the analysis of the primary endpoint. If the investigational device offers a clinically significant improvement in safety, however, a superiority delta level of zero in the evaluation of the effectiveness endpoint may be appropriate.

H. Sample Size

We recommend your protocol include the calculation of the estimated sample size appropriate to test the statistical hypothesis. For this calculation, we recommend using a statistical method that is consistent with the proposed statistical hypothesis. You should state and support all statistical assumptions associated with the sample size calculation. For additional recommendations, see **Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices**[28] and **Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials**.[29]

Since patient dropout and other forms of missing data may occur in any clinical study, we recommend adjusting the calculated sample size upward by the anticipated loss to follow-up rate. Additionally, upward adjustment of the sample size may reduce the chance of having inadequate statistical power due to incorrect assumptions regarding the treatment and placebo effects and their variance.

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[27] 21 CFR 814.82(a)(2)

[28] http://www.fda.gov/cdrh/ode/odeot476.html

[29] http://www.fda.gov/cdrh/osb/guidance/1601.html

I. Patient Selection Criteria

We recommend your protocol clearly define and support the patient population proposed for study enrollment. Important considerations include, but are not limited to:

- the category of incontinence (e.g., stress urinary incontinence due to hypermobility, stress urinary incontinence due to ISD, urge incontinence);
- prior incontinence history (e.g., duration and severity of incontinence, prior treatments or surgery for incontinence);
- general medical history (e.g., comorbidities, confounding conditions);
- gender (i.e., female only, male only, both females and males); and
- age range.

An important consideration is whether to define the eligible patient population broadly or narrowly. There is no universal approach to this issue, as each has potential advantages and disadvantages that you should carefully weigh. Designing the study to enroll a broad patient population potentially increases the enrollment rate and the device use may be studied over a wide range of subjects. However, a broadly defined patient population can result in the enrollment of patients with a wide variety of confounding factors, which can add significant variability and negatively affect the data analysis.

For example, while many devices are designed for either the male or female anatomy, some devices implanted near the bladder (e.g., injectable bulking agents, artificial urinary sphincter, electrical stimulators) may be used for treating both male and female incontinence. If a device is designed for or studied in only one gender, its indication will be limited to that population. However, if a device can be used for treating both male and female incontinence and is studied in both sexes, a single study may become difficult to analyze and interpret due to the potential confounding effect of gender, related, for example, to different mechanisms and severity of incontinence and differences in surrounding anatomy. In investigations of urinary incontinence devices, we believe permitting the enrollment of both genders in the same study (instead of enrollment of men in one study, women in another) could confound interpretation of study outcomes by reducing the overall observed safety and effectiveness of the device and obscuring the specific subpopulation that actually benefits from device use. Post-hoc subgroup analyses of broadly defined patient populations are typically more subject to bias than prospectively defined analyses of narrower patient populations.

Alternatively, defining the patient population narrowly may result in a homogeneous population that may be straightforward to analyze. A homogeneous population may also lead to a small sample size, since the variability in the responses to treatment will likely be reduced. Lastly, a patient population that is recruited with more stringent entry criteria may

minimize placebo effect.[30] However, studying a narrow patient population could slow the rate of enrollment and restrict the device's indications for use.

Therefore, we recommend your study design address the potential impact of the choice of patient population. The recommendations below are intended to help you adequately describe the target patient population and ensure the study subjects accurately reflect your description.

1. **Inclusion Criteria**

   Diagnosis

   Investigators should diagnose subjects as having the specific category (or one of the categories) of urinary incontinence for which the device is indicated. The diagnostic criteria specified in the protocol should be consistent with the current standard of care.

   Severity

   We recommend your protocol specify an objectively measured severity of incontinence that reflects the targeted patient population (e.g., minimum baseline pad weight as measured by a 1-hour pad weight test and on three 24-hour pad weight tests, minimum average number of baseline incontinence episodes per day as determined on three 3-day voiding diaries). When multiple assessments of incontinence severity are obtained at baseline (e.g., multiple 24-hour pad weight tests), we recommend your protocol specify that the subject meet the pre-defined severity level for study inclusion on each assessment.

   Age

   The protocol should state the age range eligible for enrollment. We recommend you consider the following factors in determining this range: the typical age range associated with the particular category of urinary incontinence being studied, whether investigation of the device is appropriate for pediatric patients, and the minimum life expectancy to ensure study completion.

   Prior Treatment

   We recommend your protocol specify that subjects have failed or are refractory to more conservative therapies over a clinically meaningful period of time prior to study enrollment. Generally, the type and duration of prior failed therapies depend upon the risks and benefits of study participation. That is, studies for more aggressive investigational devices should specify longer trial periods of conservative therapies (e.g., 6-12 months of failed therapy prior to enrollment) than studies for lower risk

[30] J.H. Schagen van Leeuwen, R. Castro, M. Busse, B.L. Bemelmans. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms, *Eur Urol*, 2006, 50(3):440-452.

devices. This practice helps control the overall risks associated with the investigation by excluding subjects who may benefit from more conservative treatment options.

Subject Compliance and Suitability

In addition to giving informed consent in accordance with the requirements of 21 CFR Part 50, subjects should understand all the study's procedures, restrictions, and follow up duration, have life expectancies greater than the study period, be capable of tolerating the procedure (e.g., good surgical candidate, where appropriate), and agree to the baseline and follow-up evaluations specified in the protocol.

2. Exclusion Criteria

Confounding Conditions

Your protocol should exclude subjects who have a history of any condition, illness, or surgery that might confound the results of the study. Confounding conditions include, but are not limited to, the following examples:

- categories of urinary incontinence other than the categories being investigated;
- prominent (i.e., greater than stage II as defined by the International Continence Society[31]) pelvic organ prolapse[32,33] (e.g., cystocele, rectocele);
- neurological disorders (e.g., multiple sclerosis, Parkinson's disease);
- abnormal bladder capacity (i.e., greater than 300 cc);
- abnormal post void residual (i.e., greater than 50 cc);
- urethral stricture and bladder neck contracture;
- spastic bladder;
- urinary tract infection (UTI);
- vesicoureteral reflux
- bladder stones;
- bladder tumors; and
- morbid obesity.

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[31] B.L. Shull, G. Hurt, J. Laycock, et al., "Physical Examination," in Incontinence, Edited by P. Abrams, L. Cardozo, S. Khoury, and A. Wew , Paris: Health Publication Ltd., 2002, pg. 377

[32] S. Hunskaar, K. Burgio, A. Clark, et al., "Epidemiology of urinary and faecal incontinence and pelvic organ prolapse," in Incontinence: Basics and Evaluation, edited by P. Abrams , L. Cardozo, S. Khoury, and A. Wein, vol. 1, Paris: Health Publication Ltd., 2005, pp. 290-297.

[33] R.M. Ellerkmann, G.W. Cundiff, C.F. Melick, et al., Correlation of symptoms with location and severity of pelvic organ prolapse," *Am J Obst Gynecol*, 2001, 185(6):1332-1338.

Conditions Posing Additional Risks

Depending upon the particular urinary incontinence device being studied, certain underlying conditions may pose unreasonable risks to the subject and should be excluded. Examples include, but are not limited to: concurrent infection (e.g., UTI, cystitis, urethritis), coagulation abnormalities, abnormal kidney function, and uncontrolled diabetes.

Concurrent Medication

Subjects who are taking medication that affects urination should either be excluded or adequately supported (e.g., medically necessary, stable dosage). Such medication may include prescription drugs, over-the-counter drugs, or dietary supplements (including herbal supplements and those taken as teas). If potentially confounding medications are clinically appropriate to take concurrently with the study, the protocol should request that the dosage not change during the study period unless medically necessary.

Pregnancy

Due to the potential for unknown risks to expectant women and their fetuses and offspring, we recommend that your study exclude women who are pregnant, lactating, or desiring to become pregnant during the next 12 months (including women of child-bearing potential who are not taking precautions to avoid pregnancy).

Prior Treatment

Depending upon the particular urinary incontinence device being studied, certain prior incontinence treatments may confound the study results and, therefore, should be excluded. For example, subjects treated previously with a device type similar to the one under investigation (e.g., injectable bulking agent) may be at greater risk of experiencing adverse events or have less potential for benefit.

Contraindications and Warnings Related to the Control Therapy

Subjects who would be excluded from treatment with the control therapy due to its labeled or known contraindications and warnings (e.g., hypersensitivity to the control injectable bulking agent) should be excluded.

J. Pre-Treatment Evaluation

We recommend your protocol clearly describe all baseline tests, measurements, and examinations you plan to conduct at the pre-treatment evaluation. To ensure consistency across the investigators and investigational sites, your protocol should specify clearly defined, well-recognized measures for all tests and measurements. The pre-treatment evaluation should document all of the inclusion and exclusion criteria contained in the study protocol, such as (1) confirming the diagnosis of the category of urinary incontinence under study, and (2) ruling out any significant coexisting disease or condition that might put the subject at increased risk or confound the data analysis.

We recommend your protocol specify the collection of the following information at the pre-treatment evaluation.

1. Medical History

We recommend your protocol instruct investigators to perform a thorough medical history, focused on the subject's urinary incontinence. The purpose of the medical history is to evaluate the subject's eligibility for the study and to rule out confounding factors. To permit future analyses of the contribution of various patient factors to the study results, investigators should record detailed medical history information in the case report forms. We recommend that the medical history include, but not be limited to:

- dates and types of prior surgeries for problems other than urinary incontinence;
- information regarding prior or ongoing therapies for urinary incontinence (e.g., surgeries, medications, device treatments, pelvic floor exercise therapy, biofeedback, electrostimulation therapy), such as: treatment type, dates of therapy, duration, outcome, and side effects experienced;
- dates of past bladder or kidney infections;
- a detailed record of all medication (over-the-counter and prescription) and dietary/herbal supplements taken over the previous 6 months, indicating those currently being taken and their dosages;
- description of the method currently being used by the subject to manage urinary incontinence;
- vaginal parity, if applicable;
- menopausal status, if applicable;
- history of allergies;
- history of current or past malignancy; and
- documentation of other conditions that could be affected by treatment (e.g., autoimmune diseases for devices that use materials of animal origin) or that could affect or confound treatment outcome.

Those potential study subjects found to have urinary incontinence based on the medical history described above should undergo the evaluations listed below to confirm the diagnosis of the specific urinary incontinence category being investigated and to exclude pelvic organ prolapse or neurologic disorders as the predominant factors causing urinary incontinence.

2. Physical Examination

We recommend your protocol instruct investigators to perform a physical examination, including a detailed urological history, to assess urinary symptoms and symptoms of bowel function, sexual function, and, in females, pelvic organ prolapse.

3. Neurological Examination

We recommend investigators perform a simple neurological examination on all the patients, including assessment of anal sphincter tone, evaluation of voluntary anal contractions, and evaluation for intact perineal sensation. If abnormalities are noted which would confound the study results, the investigator should exclude the subject from study participation.

4. Voiding Diary

To document the frequency and severity of urinary incontinence and the circumstances under which urine leakage occurs, we recommend that subjects complete voiding diaries. Voiding diaries should document the daily chronological record of fluid intake, incontinence episodes with associated activity and perceived level of urgency, severity of each incontinence episode (i.e., estimated volume of leakage), pad usage, and normal voiding episodes with measured volume. To maximize the quality of the collected information, we recommend that investigators provide subjects with adequate instructions on completing the voiding diary and train them on how to collect this information.

Due to the high within-patient variability associated with urinary incontinence, acquiring a stable baseline measure is difficult using a single voiding diary. Therefore, we recommend collecting three 3-day voiding diaries (i.e., three diaries, each of three days duration) during the pre-treatment evaluation.

5. Pad Weight Testing

We recommend your study include pad weight testing to document quantitatively the severity of urine leakage at baseline. Two commonly used methods of measuring urine leakage using pad weight are:

- the 1-hour in-clinic provocative pad weight test; and
- the 24-hour in-home pad weight test.

The subject generally performs the 1-hour provocative pad weight test in the doctor's office under prescribed exercises, whereas the subject performs the 24-hour pad weight test at home, by going about his or her normal daily activities (all pads used during the 24-hour period are collected and weighed). Although a 1-hour provocative pad weight test is inherently more standardized than the 24-hour pad weight test, it does not incorporate activities of daily living, which affect the patients' quality of life. However, the 1-hour provocative pad weight test specifically targets stress urinary incontinence and can be used to aid in making a differential diagnosis, whereas the 24-hour pad weight test is generally applicable to all categories of urinary incontinence. Therefore, we recommend performing both types of pad weight tests. To ensure consistency within and between subjects, we recommend your protocol standardize both types of pad weight tests to the extent possible. Female subjects should not undergo pad weight testing during menses.

Due to the high within-patient variability associated with urinary incontinence, acquiring a stable baseline measure is difficult using a single 24-hour pad weight test. Therefore, we

recommend performing three 24-hour pad weight tests during the pre-treatment evaluation.

6. Urodynamics Testing

We recommend you perform the following baseline urodynamics tests at the pre-treatment evaluation to confirm the diagnosis of the specific urinary incontinence categories being investigated and to rule out abnormal bladder function.

Uroflowmetry

Uroflowmetry should include a measure of voided volume above a predefined minimum amount (e.g., 125 cc),[34,35] total time of voiding, peak urine flow rate, average urine flow rate, and post-void residual urine volume (PVR). Either ultrasound or catheterization is appropriate to measure PVR, but you should use the same method pre- and post-treatment.

Leak Point Pressure

Leak point pressure (LPP) is the minimum intravesical pressure at which urine leaks around a small, pressure-sensing urethral catheter. LPP is determined by inserting a catheter into the bladder and filling it with 200-250 cc of water, and should be used as part of the subject's work-up to identify the presence or absence of stress urinary incontinence.[36,37] LPP is usually low (less than 50-60 cm H_2O) for patients whose stress urinary incontinence is predominantly due to ISD. Therefore, for studies targeting stress urinary incontinence due to ISD, we recommend your protocol's inclusion criteria specify a maximum LPP for study entry.

Cystometry

Liquid cystometry (using saline) should include a measure of bladder capacity, sensation of fullness (compliance), and urgency (volume at which involuntary leakage occurs). In addition to being a useful test for documenting normal bladder function, you should also include cystometry as part of the subject's work-up to identify the presence or absence of urge incontinence.

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[34] P. Abrams, Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function, *BJU Int*, 1999, 84:14-15.
[35] J.G. Blavias and A. Groutz, Campbell's Urology, edited by P.C. Walsh, A.B. Retik, E. Darracott Vaughan Jr., et al., Philadelphia: Saunders, 2002, 8th edition, vol. 2, pp. 1039.
[36] R. A. Appell, Injectables for urethral incompetence, *World J Urol*, 1990, 8(4):208-211.
[37] E.J. McGuire, C.C. Fitzpatrick, J. Wan, et al., Clinical assessment of urethral sphincter function, *J Urol*, 1993, 150(5 Pt 1):1452-1454.

7. Cystoscopy

Your protocol should instruct investigators to perform cystoscopic examination at the pre-treatment evaluation to document the absence of bladder neck obstruction, presence or absence of urethral strictures, and other bladder pathology.

8. Laboratory Testing

Your protocol should instruct investigators to perform the following laboratory tests to screen the subject for study entry.

Urinalysis with Urine Culture

Investigators should perform urinalysis with urine culture to exclude patients with active UTI.

Blood Chemistry

We recommend your protocol specify the collection of routine blood chemistry information, including complete blood count (CBC) and blood urea nitrogen (BUN).

Pregnancy Test

To screen subjects for pregnancy, investigators should administer a pregnancy test to women of child-bearing potential.

9. Questionnaires

Your protocol should instruct investigators to administer the following questionnaires to study subjects.

Quality of Life

Subjects should complete a validated, incontinence-specific quality of life assessment. The purpose of this questionnaire is to assess subject perceptions of the impact of treatment upon various aspects of their lives.

Sexual Function

Subjects should complete a validated, gender-specific sexual function questionnaire prior to treatment, to enable assessment of whether device use impacts sexual function.

Patient Satisfaction

Subjects should complete a standardized survey to record their satisfaction with specific aspects and dimensions of their lives that may be impacted by urinary incontinence. We recommend you compare these baseline results to the results of the post-treatment satisfaction survey.

K. Investigator Selection and Training

We recommend you select study sites and investigators that are capable of recruiting sufficient numbers of eligible subjects representative of the target population for your device. Sites that have a large proportion of protocol deviations can complicate pooling and statistical analysis of the results, and ultimately may invalidate the study conclusions.

Many investigational devices for urinary incontinence are novel in design or clinical application, or involve different techniques than used for existing devices. To help ensure the safe, proper, and consistent use of the investigational device, and to enhance the ability to pool the data across study sites, we recommend your protocol describe a training program to educate investigators on the use of your device. This training should consist of didactic instruction, covering the device functions and principles of operation, and may also involve proctoring by an experienced physician. Additionally, it may be useful for the training to highlight the important or unique aspects of the clinical study, such as screening, obtaining informed consent, the randomization process, blinding, the follow-up schedule, data collection methodology, and adverse event reporting.

L. Treatment Information

To promote consistency across investigators and investigational sites, we recommend your study protocol thoroughly describe the investigational and control treatments. This information should include, but is not limited to:

- pre-operative patient education and preparation;
- anesthesia requirements;
- device directions for use (e.g., sizing, route of administration, technique, placement, amount implanted, settings or treatment parameters);
- recommended instrumentation or imaging;
- surgical technique; and
- post-operative care.

Additionally, if the investigational or control therapy involves multiple or staged treatments, or if the protocol allows the option of retreatment during the study, your protocol should describe these aspects of treatment in detail. In the case of retreatment, we recommend your protocol specify the criteria for retreatment, the minimum and maximum time intervals between treatments, and any special treatment instructions for performing retreatment.

M. Post-Treatment Evaluations

Your protocol should clearly describe the follow-up schedule, and identify all tests, measurements, and examinations you plan to conduct at each post-treatment evaluation. The follow-up schedule should include early examinations to assess any post-operative healing period and the initial use of the device, in addition to regular visits throughout the follow-up period to collect outcome information to allow assessment of the primary and secondary endpoints. To ensure consistency during the study and across investigational sites, we

recommend your protocol instruct investigators to perform post-treatment tests using the same methodology as used during the pre-treatment evaluation.

We recommend that the post-treatment evaluations include, but not be limited to, the following tests and assessments:

- physical examination;
- voiding diary;
- pad weight testing; and
- questionnaires.

In addition, we recommend your protocol specify the following tests and assessments during the post-treatment evaluation period.

Urodynamics Testing

For a device that has the potential to impact bladder emptying, we recommend assessing PVR at each post-treatment exam. For an indication of stress urinary incontinence, we recommend assessing LPP at 6 and 12 months post-treatment. For an indication of urge incontinence, we recommend performing cystometry at 12 months post-treatment.

Cystoscopy

For an intravesical or intraurethral device, we recommend cystoscopic examination at 12 months post-treatment; for other device designs, we recommend that cystoscopic examinations be scheduled at appropriate times post-treatment to assess the potential impact of the device upon the bladder and urethra.

Laboratory Testing

To assess for UTI, we recommend performing urinalysis at each follow-up visit, with urine culture if indicated. Additionally, we recommend collecting blood chemistry information at 12 months post-treatment, including CBC and BUN.

N. Statistical Analysis Recommendations

Your protocol should include a comprehensive statistical analysis plan that prospectively describes how the study results will be analyzed. All statistical analyses used in an investigation should be appropriate to the analytical purpose and thoroughly documented. We recommend your statistical analysis plan include the information described below. However, depending on the design or indications of your device, or the nature of the data you have collected, FDA may recommend additional or different analysis techniques.

1. Primary Endpoint Analyses

The primary statistical analysis of the study is generally the statistical analysis used to assess the overall success or failure of the study. Therefore, we recommend describing and documenting the details of this analysis in your protocol. As stated under **F. Study Duration**, we recommend conducting the primary analysis of study success using 12-

month follow-up data. To reduce bias, we recommend performing this primary analysis using the intent-to-treat (ITT) population. The ITT population includes all subjects randomized into the study, regardless of whether or not the subjects received the treatment to which they were randomized.

In addition to the ITT analysis, we recommend your protocol specify other analyses of the primary endpoint to assess the robustness of the study results. We recommend you conduct these additional analyses to assess whether the results are consistent with the conclusion of the primary ITT analysis, and, therefore, are supportive of your study conclusions. Every effort should be made to assess the plausibility of the underlying assumptions for each of these sensitivity analyses. We recommend these additional analyses include the following, among others:

- analysis of the per protocol population (e.g., subjects treated and followed per the protocol);
- sensitivity analyses, using a variety of pre-specified methods for imputing missing data;
- longitudinal or repeated measures analysis, to assess impact of "time post-treatment" upon the results; and
- assessment of the number of subjects who are "dry," "significantly improved," "not significantly improved," and "worse" at each follow-up period (relative to baseline).

To investigate the potential impact of subject-related and treatment-related factors upon the primary safety and effectiveness endpoints and to uncover any important prognostic factors, we recommend the protocol describe comprehensive covariate analyses. To minimize bias associated with these analyses, we recommend your protocol prospectively define all important covariates. Important covariates include, but are not limited to:

- investigational site;
- gender;
- age;
- weight or body mass index;
- ethnicity;
- smoking status;
- alcohol use status;
- occupation;
- duration of incontinence;
- all baseline measures of incontinence, including incontinence-specific quality of life score;
- vaginal parity, if applicable;
- menopausal status, if applicable;

- prior hysterectomy, if applicable;
- prior surgery for incontinence;
- retreatments;
- medication usage; and
- device-related covariates (e.g., device settings).

2. Secondary Endpoint Analyses

We recommend your protocol prospectively define the statistical plan for performing secondary endpoint analyses in the event that the primary endpoint analysis has been successfully met. If the secondary endpoint analyses are intended purely as exploratory analyses, or are not intended to support the indication for use or device performance, we recommend you submit only simple descriptions of the analyses. If, on the other hand, any of the secondary endpoint analyses are intended to support the indication for use or the performance of your device in the labeling (e.g., comparing treatment and control groups using p-values or confidence intervals), we recommend you pre-specify this intention in your study protocol and describe in detail the statistical methods you plan to follow.

The primary statistical challenge in supporting the indication for use or device performance in the labeling is in making multiple assessments of the secondary endpoint data without increasing the type 1 error rate above an acceptable level (typically 5%). There are many valid multiplicity adjustment strategies available for use to maintain the type 1 error rate at or below the specified level, three of which are listed below:

- Bonferroni procedure;
- Hierarchical closed test procedure; and
- Holm's step-down procedure.

Because each of these multiplicity adjustment strategies involves balancing different potential advantages and disadvantages, we recommend you prospectively state the strategy that you intend to use. We recommend your protocol prospectively state a statistical hypothesis for each secondary endpoint related to the indication for use or device performance.

3. Missing Data

Missing data can represent a significant source of potential bias. Although a variety of statistical methods exist for imputing missing data, excessive missing data can introduce an unacceptable level of uncertainty in the results and invalidate the study conclusions. Therefore, we recommend every effort be made to minimize the incidence of missing data.[38] To this end, we recommend your protocol incorporate the elements listed below.

[38] R.H. Woolhard, K. Carty, P. Wirtz, R. Longabaugh, et al., Research fundamentals: follow-up of subjects in clinical trials: addressing subject attrition, *Acad Emerg Med*, 2004, 11(8):859-866.

Efforts to minimize missed visits and drop-outs

We recommend you describe the special efforts to monitor and minimize the incidence of missing data and patient drop-outs during the study, such as monitoring activities, instruction and training on voiding diary data collection, special incentives to subjects for study compliance, methods to remind subjects of scheduled visits, and specific efforts to contact subjects who miss their visits (e.g., telephone calls, post cards, contact next-of-kin).

Efforts to document the reasons for missing data

We recommend you identify the steps to document:

- the reason for each missed visit (e.g., complications, difficulty getting transportation to the site);
- the reason for each drop-out (e.g., seeking alternate therapy, complications or intolerance to the device, dissatisfaction with the device, moved away); and
- the cause of any death (e.g., autopsy report, death certificate).

To permit a complete and detailed accounting of all study subjects, we recommend you collect complete information during the study. Because loss to follow-up jeopardizes the conclusions that can be made about the long-term safety and effectiveness of a device, you should attempt to minimize the overall rate of loss to follow-up over the course of the study.

The protocol should specify how you plan to address missing data in the statistical analysis. A common approach is ITT analysis. Other approaches include the as-treated or per protocol analyses. The ITT approach preserves the comparability of patients with respect to (observed and unobserved) baseline characteristics and is generally regarded as the preferred method for evaluating a new therapy.[39] As discussed above (in **1. Primary Endpoint Analyses**), sensitivity analyses that compare results obtained under various assumptions about the missing data mechanism should be conducted.

O. Risk Analysis

The protocol should contain a clinically sound risk analysis in support of the proposed investigation. In clinical studies that require an approved IDE application,[40] the risk analysis must include the elements specified in 21 CFR 812.25(c), which are listed below:

- a description and analysis of all increased risks to which subjects will be exposed by the investigation;

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[39] J.H. Ellenberg, Intent-to-treat analysis versus as-treated analysis, *Drug Inf J*, 1996, 30:535-544.

[40] An approved IDE is required before beginning a clinical study of a significant risk device in the United States as defined in 21 CFR 812.3(m).

- the manner in which these risks will be minimized;
- a justification for the investigation; and
- a description of the patient population, including the number, age, sex, and condition.

We recommend the risk analysis section of your protocol include the risks of the device itself (e.g., unintended electrical shock from an implantable stimulator, or tissue burns occurring during the use of an electrosurgical heating device), and the risks associated with the treatment procedure (e.g., the surgical risks associated with the placement of an implant, the risks of cystoscopy associated with the use of an injectable bulking agent, or anesthesia risks). In addition, we recommend you convey these risks to potential subjects using easily understood terminology in the informed consent document.

P. Study Monitoring

We believe that proper study monitoring is critical to assure the safety of study subjects, investigator adherence to the investigational plan, and the quality and integrity of the resulting clinical data. Therefore, we recommend that the investigational plan incorporate a comprehensive, written monitoring plan that investigators agree to follow during the study. In clinical studies that require an approved IDE application, the IDE application must include written monitoring procedures in accordance with 21 CFR 812.25(e). In addition, please see the Agency's guidance entitled **Guideline for the Monitoring of Clinical Investigations**[41] on recommended approaches to monitoring clinical investigations involving FDA-regulated products.

Written monitoring procedures help to assure that each person involved in the monitoring process carries out his or her duties. In addition to the elements required by 21 CFR Part 812 and 21 CFR Part 50 and the recommendations of the **Guideline for the Monitoring of Clinical Investigations**, we recommend you incorporate the following elements into your monitoring procedures, including, but not limited to:

- identification of a trained and qualified monitor;
- description of pre-investigation and periodic visits, including the timing of these visits and the specific monitoring activities to be performed;
- criteria for the review of representative subject records for completeness and accuracy; and
- elements for an adequate record of on-site monitoring visits, including findings, conclusions, and action taken to correct any deficiencies.

We recommend the study monitor overseeing the trial identify potential weaknesses during the study that may necessitate modifying the protocol. The study monitor should also have contingency plans available for unforeseen problems and a means to implement rapidly those

[41] http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html

plans. You and the monitor should carefully devise contingency plans for the study with the goal of preserving the integrity of your study design. We also recommend your monitor assure that study subjects are entered, interventions assigned, follow-up data collected at the appropriate times, and data are completely and accurately recorded, as specified in the protocol.

Q. Case Report Forms

To assure all information collected during the course of the clinical study is documented, we recommend your study incorporate case report forms for investigators to complete separately for each subject. To facilitate the documentation of all subject, treatment, and study data, we recommend you format these forms to instruct investigators to record all information described in your protocol. The case report forms should include, but not necessarily be limited to:

- a pre-treatment evaluation form;
- a treatment information form;
- post-treatment evaluation forms;
- a concomitant medication form;
- a protocol deviation form;
- an adverse events form; and
- a patient discontinuation information form.

FDA's recommendations for the content of each form are discussed below.

A pre-treatment evaluation form should include all relevant information from the pre-treatment evaluation, such as medical history, physical exam, baseline screening measures, and documentation of inclusion and exclusion criteria.

A treatment information form should include all relevant information regarding the treatment procedure for both the investigational device and the control therapy, such as date, pre-operative preparation, anesthesia usage, device directions for use (e.g., sizing, route of administration, technique, placement, amount implanted, settings or treatment parameters), instrumentation and imaging usage, surgical technique, post-operative care, protocol deviations, and complications. If retreatment is permitted during the study, similar information should be recorded at that time.

Post-treatment evaluation forms should include all data collected at each follow-up visit. Generally, a separate post-treatment evaluation form should be completed at each follow-up visit.

A concomitant medication form should list all medications and dietary supplements taken by the subject at baseline and during the study, and specifies the dates of usage and dosage.

A protocol deviation form should identify and describe each protocol deviation, indicating the date, type of deviation, and clinical justification for the deviation.

An adverse events form should identify and describe each adverse event, including the onset date, type and description, device-relatedness, severity, method of intervention or resolution, and resolution date.

A patient discontinuation information form should include the date and reason for patient discontinuation from the study. Typical reasons for study termination include study follow-up completed, consent withdrawn by subject, exited to receive alternate treatment, exited by investigator, death, and lost to follow-up.

Appendix 1

Sources of Bias	Common Mitigation Methods
Selection Bias occurs when patients possessing one or more important prognostic factors appear more frequently in one of the comparison groups than in the others.	• Randomization • Objective diagnostic and outcome measures • Homogeneous study population • Pre-specified protocol, endpoints, and statistical plan
Investigator Bias occurs when an investigator consciously or subconsciously favors one study group at the expense of the others.	• Blinding • Pre-specified protocol, endpoints, and statistical plan
Evaluator Bias is a type of investigator bias in which the person measuring the outcome variable intentionally or unintentionally records the measurements in favor of one intervention over another. Studies that have subjective endpoints (e.g., quality of life) are particularly susceptible to this form of bias.	• Blinding • Objective diagnostic and outcome measures
Placebo or Sham Effect is a bias that occurs when a patient exposed to an inactive therapy believes that he (or she) is being treated with an intervention and subsequently shows or reports improvement.	• Randomization • Blinding • Objective diagnostic and outcome measures
Missing Data can introduce bias when subjects who do not report for follow-up experience a different outcome from those who do.	• Documentation and enhanced compliance • Plan to conduct sensitivity analyses