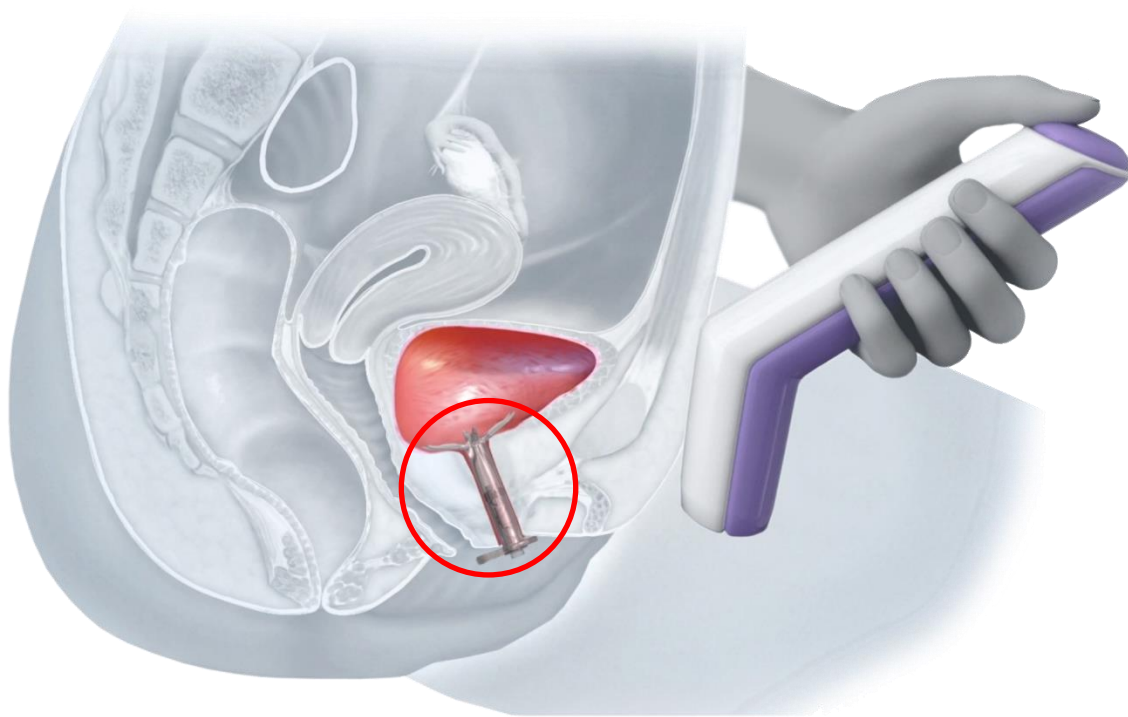




Evidence Dossier:
inFlow™ Urinary Prosthesis

FDA De Novo Approval No. DEN130044



**For Women with Permanent Urinary Retention
Resulting from Impaired Detrusor Contractility (IDC) of Neurologic Origin**

Medical Reviewers

As board-certified urologists with both academic and clinical expertise in voiding dysfunction, we have reviewed the Medical Technology Dossier for the inFlow Urinary Prosthesis and conclude that based on moderate quality, moderate certainty evidence the benefits of the InFlow Urinary Prosthesis outweigh the risks and it should be a recommended medical option for women with chronic urinary retention.

Our determination of this Dossier's quality of evidence is based on American Urological Association Guidelines Concerning Level of Certainty and Evidence Strength, summarized on the next page.

Michael B. Chancellor, M.D.

Director of Aikens Neurourology Research Center in the Dept. of Urology, Oakland University William Beaumont School of Medicine, Royal Oak, MI - Fellowship in Neurourology and Female Urology

Israel Franco, M.D., FACS, FAAP

Clinical Professor of Urology; Director of Yale-New Haven Children's Bladder and Continence Program; Director of Yale Medicine Pediatric Bladder & Continence Program

Karny Jacoby, M.D.

Urologist at University of Washington Medical Center - Subspecialty boarded in Urology and in Female Pelvic Medicine and Reconstructive Surgery and also boarded as a Certified Principal Investigator

Kathleen C. Kobashi, M.D., FACS, FPMRS

Program Director of Urology Resident Program, Head of Urology and Renal Transplantation Section and Director of Pelvic Floor Center at Virginia Mason Medical Center, Seattle, WA

Eric S. Rovner, M.D.

Director of the Voiding Dysfunction, Female Urology and Urodynamics Section in the Department of Urology at Medical University of South Carolina and past president of Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction

Richard A. Schmidt, M.D.

A leading authority on neurogenic bladder, co-inventor of the Medtronic InterStim® and patent holder for use of Botox® for neurogenic overactive bladder

Roger R. Dmochowski, M.D.

Professor at the Department of Urology, Vice Chair of the Department of Surgical Sciences at Vanderbilt University in Nashville and Clinical Assistant Professor in Surgery at the Uniformed Services University of the Health Sciences in Bethesda, Maryland

Michael S. Ingber, M.D.

Director of Urogynecology and General Urology at Morris Urology, Denville NJ - Fellow in Female Pelvic Medicine and Reconstructive Surgery/Urogynecology, Glickman Urological and Kidney Institute

Michael J. Kennelly, M.D., FACS, FPMRS

Co-Director of the Women's Center for Pelvic Health and Medical Director of the Charlotte Continence Center at Carolinas Rehabilitation - Specialty Certification in Female Pelvic Medicine and Reconstructive Surgery

Brian P. Murray, M.D.

Director of Urology, St. Peter's Health Partner Medical Associates, Female Pelvic Medicine and Reconstruction Surgery, Albany NY - Specialty Certification in Female Pelvic Medicine and Reconstructive Surgery

Matthew P. Rutman, M.D.

Director of Voiding Dysfunction, Incontinence and Female Urology at Columbia University Medical Center, Associate Professor of Urology at CUMC and Director of the Female Urology and Voiding Dysfunction Fellowship

Steven W. Siegel, M.D.

Director of the Metro Urology Centers for Female Urology and Continence Care. Previously, Head of the Section of Female Urology and Urodynamics at the Cleveland Clinic in Cleveland, Ohio

American Urological Association Guidelines Concerning Level of Certainty and Evidence Strength

Quality of Individual Studies and Determination of Evidence Strength. The quality of individual studies is assessed using accepted criteria to determine the quality of internal and external validity.

The categorization of evidence strength (ES) is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes and generalizability of samples, settings and treatments for the purposes of the guideline. AUA categorizes evidence strength as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data).

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength and the judgment regarding the balance between benefits and risks/burdens per the following table:

Standard	Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence
Recommendation	Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence
Option	Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B or C evidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A (high level of certainty) or Grade B (moderate level of certainty) evidence. Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C (low level of certainty) evidence. Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or unclear; Options may be supported by Grade A (high certainty), B (moderate certainty) or C (low certainty) evidence. Options generally reflect the reviewer's judgment that a particular decision is best made by the clinician who knows the patient with full consideration of the patient's prior treatment history, current quality of life, preferences and values.

Table of Contents

Executive Summary	1
1 Burden of Illness	3
1.1 Clinical Characteristics and Presentation of Medical Condition.....	3
1.2 Epidemiology.....	3
1.3 Clinical.....	5
1.3.1 Major Adverse Health Outcomes Associated with Medical Condition	5
1.4 Unmet Need	5
1.4.1 Description of Unmet Need.....	5
1.4.2 How the inFlow Addresses Unmet Need.....	5
1.4.3 Indicated Patients	7
1.4.4 Fit in Clinical Pathway.....	7
2 Product Information	8
2.1 Technology Description and Characteristics	8
2.2 Device Classification and Approval Status	8
2.3 Procedure Codes	9
2.4 Device Components and Specifications	9
3 Value Evidence Supporting TECHNOLOGY	10
3.1 Clinical Efficacy and Patient Outcomes.....	10
3.1.1 Pivotal Trial, A Comparison to the Present Standard of Care.....	10
3.1.2 Non-Comparative Clinical Studies.....	16
3.2 Core Value Drivers.....	19
3.2.1 Urinary Tract Infections (UTIs).....	20
3.2.2 Quality of Life (QoL).....	21
3.2.3 Encrustation	22
3.3 Quality of Life Outcomes.....	23
3.3.1 Core Value Drivers.....	23
3.3.2 Role of TECHNOLOGY in Improving Patient Quality of Life.....	24
3.3.3 Device Safety Profile.....	24
4 Future Directions and Applications	25
4.1 Emerging Clinical Applications.....	25
References Cited in Section 3.2	26
Exhibits	
A. inFlow Animal Studies and Laboratory Testing	28
B. Comparison of Approved Devices for Chronic Bladder Management.....	32
C. inFlow Risk/Benefit Analysis	37
Attachments	
1. inFlow Instructions for Use	
2. inFlow Clinical Publications	

Executive Summary

The inFlow™ Intraurethral Valve-Pump and Activator (collectively, the inFlow Urinary Prosthesis) is a unique intervention for use by women with impaired detrusor contractility (IDC) of neurologic origin, which results in permanent urinary retention. This is a generally incurable condition and there are no perfect solutions. The inFlow cannot help all women with IDC, but the majority of suitable device candidates are easily identified and the inFlow can provide these women with significant therapeutic benefits (in most cases at less cost than currently covered urinary catheters):

- **Safety:** The inFlow has an excellent safety profile. Its pivotal trial showed the inFlow have a lower infection rate than intermittent catheters, the current standard of care. Reducing catheter-associated infection (CA-UTI) is recognized by CMS and many others as one of the highest priorities in healthcare. No serious or long-lasting adverse events associated with inFlow use have been reported and those that have occurred have been remedied by removing the device, which can be easily and safely done, even by patients.
- **Quality of Life:** For most device users, this is the inFlow's most tangible benefit. As shown in **Table 1**, the inFlow can restore function and personal dignity to women in acute need:

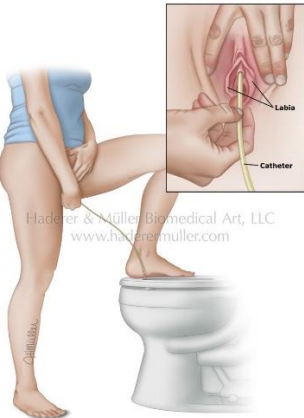

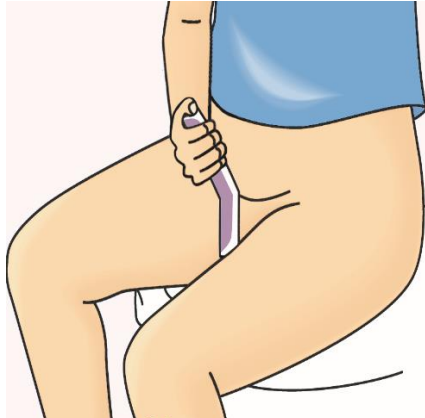
Intermittent Catheters	Indwelling (Foley) Catheters	inFlow Urinary Prosthesis
 <p>Requires insertion of a tube into the bladder and passively draining urine into a toilet 4-6+ times per day</p>	 <p>Requires being tied to a bag of your own urine and enduring an exceedingly high infection rate</p>	 <ul style="list-style-type: none"> ▪ Allows almost normal use of a toilet ▪ Eliminates tubes and bags, improving body image and hygiene ▪ Allows most users to void without assistance, increasing self-reliance

Table 1. Comparison of Bladder Drainage Methods

The American Urological Association and major patient advocacy groups have requested that CMS make inFlow a covered benefit as a much-needed alternative to currently covered urinary catheters.

Indication for Use: The inFlow Intraurethral Valve-Pump and Activator is a replaceable urinary prosthesis intended for use in female patients 18 years of age or older who have incomplete bladder emptying due to impaired detrusor contractility (IDC) of neurologic origin, and who are capable of operating it in accordance with instructions or who have trained caregivers. The device must be replaced every 29 days (or less).

IDC Background: Women with IDC are unable to spontaneously urinate due to insufficient detrusor muscle contraction. Their condition is most often a consequence of life-altering neurologic disease or injury such as multiple sclerosis, Parkinson's disease, spinal cord injury, spina bifida, stroke, diabetes or pelvic surgery. IDC is itself a serious medical problem and complications include urinary retention, overflow urinary incontinence, recurrent UTIs, bladder stones and impaired renal function.

Current Treatments: Due to its neurologic origin, IDC is generally incurable and there are few clinical options. While new procedures (the Medtronic InterStim® and Allergan Botox®) provide alternatives for neurogenic *overactive* bladder, none have emerged for neurogenic *underactive* bladder, i.e. IDC. The vast majority of women with IDC must use urinary catheters for bladder drainage.

Urinary catheters may be the most commonly used of all medical devices; however, with chronic use they routinely cause serious problems, notably: 1) urinary tract infections (UTIs), 2) low quality of life (QoL), and 3) encrustation. These problems are acutely heightened for women with IDC, since they must use urinary catheters every day for the rest of their lives.

Core Value and Supporting Evidence: As a urinary prosthesis, the inFlow's clinical objective is to restore as much voiding function as possible. Women with IDC cannot generate bladder pressure, so the inFlow pumps their urine out, allowing almost normal use of a toilet. In mimicking normal urination, the inFlow maintains the three essential elements required for bladder health: periodic, forceful and complete evacuation of the urine. (In comparison, an indwelling urinary catheter maintains none of these.) As a result of these and other factors and as shown in **Table 2**, the inFlow provides superior performance in the areas where urinary catheters are known to be deficient:

Infection (UTI)	The inFlow's pivotal trial (<i>n</i> =157) showed it to have a lower rate of UTIs than clean intermittent catheterization (CIC), the current standard of care. This was a significant enough finding that the FDA put out a news release when it approved the inFlow stating: <i>"It is noteworthy that the most significant of adverse events – UTI – appears to occur at a lower rate with the inFlow device as compared to CIC."</i>
Quality of Life (QoL)	The inFlow's pivotal trial also showed that it improved QoL by almost 60% compared to CIC (clinically and statistically significant). A smaller one-year study by Lynch <i>et al</i> showed a QoL improvement of 80%.
Encrustation	An <i>in vitro</i> study by Stickler <i>et al</i> showed inFlow to have encrustation resistance at least $\geq 8.4x$ superior to an all-silicone Foley catheter, the current gold standard. Also, no encrustation was reported in the inFlow's pivotal trial.

Table 2. Comparison of Clinical Outcomes: The inFlow vs. Current Standard of Care

As shown in **Table 3**, extensive documentation concerning the inFlow's safety and effectiveness exists in the form of scientific and clinical data from a variety of sources:

1	Post-Market Data/Reports	The inFlow has a 20-year history as a CE-marked device and cumulative clinical experience >1,200 women-years of use. There have been no reports of serious or long-lasting adverse events associated with device use.
2	Laboratory Bench Testing	As listed in Exhibit A , bench studies demonstrated that the inFlow device and Activator meet their performance specifications and, where applicable, conform to ISO, ASTM and other recognized standards.
3	Biocompatibility Testing	As listed in Exhibit A , a variety of animal studies and laboratory tests confirm that the inFlow meets current ISO 10993-1:2009 (Biological Evaluation of Medical Devices) standards for a permanent surface device with mucosal membrane contact.
4	In Vitro Study of Comparative Encrustation Resistance	As summarized in Section 3.2.3 of this document, an <i>in vitro</i> study by Stickler <i>et al</i> showed inFlow to have encrustation resistance at least $\geq 8.4x$ superior to an all-silicone Foley, the current gold standard.
5	Clinical Studies	As discussed in Section 3 of this document and as included in Attachment 2: inFlow Clinical Publications , a total of seven clinical studies (total <i>n</i> =385) of the inFlow have been published in major peer-reviewed journals, including its pivotal trial (<i>n</i> =157) and six investigator-sponsored studies (total <i>n</i> =228), three of which were long-term studies of 1-4 years.

Table 3. Summary of Safety and Effectiveness Evidence for the inFlow Urinary Prosthesis

In sum, the inFlow serves (only) a patient population with very few alternatives and there is evidence that it provides them not only with a high level of infection resistance, which is a major CMS priority, but also substantially improves their quality of life.

1 Burden of Illness

1.1 Clinical Characteristics and Presentation of Medical Condition

Women with IDC are unable to spontaneously urinate due to insufficient detrusor muscle contraction. Their condition is most often a consequence of life-altering neurologic disease or injury.

1.2 Epidemiology

Analysis Method: IDC prevalence is not reported or tracked in the U.S. and there is no government requirement to do so. In the absence of government-reported data, this analysis relies on scientifically-sound estimates of prevalence for neurologic conditions known to result in IDC and then applies the IDC prevalence for each condition. The definition used in this analysis is IDC requiring use of urinary catheters.

Per **Table 4**, the results of this analysis indicate that there are some 470,000 U.S. Women with IDC:

Neurologic Condition	No. U.S. Women	% IDC	No. IDC
Multiple Sclerosis (MS)	665,000	26.00	172,900
Diabetes	15,301,500	0.08	122,412
Spina Bifida	83,000	50.00	41,500
Parkinson's	330,000	12.50	41,250
Multiple System Atrophy (MSA)	36,274	100.00	36,274
Spinal Cord Injury (SCI)	56,400	25.00	14,100
All Other Neurologic Conditions			<u>40,000</u>
Total, U.S. Women with IDC			468,436

Table 4. Estimated Number of U.S. Women with IDC

Based on clinical experience to date, about 50% or 235,000 U.S. women are viable candidates for the inFlow Urinary Prosthesis.

Multiple Sclerosis (MS) – 172,900 U.S. Women

“Nearly 1 million people are living with MS in the U.S.”¹ Also, “The ratio of women with MS to men with the disease is 2 to 1.”² Therefore, there are ~665,000 U.S. women with MS. Urinary catheterization was reported by 26% of respondents to a 2005 NARCOMS survey of MS patients.³ Since MS is progressive, even though only 26% of respondents to this survey reported using or having used catheterization, the lifetime usage is likely to be higher; however, even 26% catheterization use would mean there are approximately 172,900 U.S. women with MS related IDC.

Diabetes – 122,412 U.S. Women

30.3 million Americans have diabetes (23.1 million are diagnosed with diabetes and 7.2 million are undiagnosed).⁴ Since women comprise 50.5% of the U.S. population, that means there are 15,301,500 U.S. women with diabetes. Bladder dysfunction is common in diabetics and it may be that up to 80% of

¹ MS Society. (2017) *Preliminary Results of MS Prevalence Study Estimate Nearly 1 Million Living with MS in the U.S.* News Release of Oct 2017. <https://www.nationalmssociety.org/About-the-Society/News/Preliminary-Results-of-MS-Prevalence-Study>

² Pietrangelo A, Higuera V, Kim S. (2015) *Multiple Sclerosis by the Numbers: Facts, Statistics, and You.* Healthline Mar 24, 2015. <https://www.healthline.com/health/multiple-sclerosis/facts-statistics-infographic>

³ Mahajan, S. T., Frasure, H. E., & Marrie, R. A. (2013) *The prevalence of urinary catheterization in women and men with multiple sclerosis.* The Journal of Spinal Cord Medicine, 36(6), 632–637. <http://doi.org/10.1179/2045772312Y.0000000084>

⁴ Centers for Disease Control and Prevention. (2017) *National Diabetes Statistics Report.* Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.

diabetics will develop diabetic cystopathy (DC).⁵ The use of the term DC in the literature varies considerably, including both overactive and underactive bladder, but is most often used to describe “hyposensate” bladder.⁶ This would indicate that there are as many as 12,241,200 women with DC; however, a urodynamics study of subjects with DC found that only 10% demonstrated “detrusor areflexia,”⁷ or IDC. This would indicate that there are 1,224,120 women with diabetic IDC; however, it is not clear that all require catheterization. Assuming even 10% do, then there are at least 122,412 U.S. women with diabetes who meet the definition of IDC used in this analysis.

Spina Bifida – 41,500 U.S. Women

“An estimated 166,000 individuals with spina bifida live in the United States” and almost all have neurogenic bladder.⁸ Assuming 83,000 are women and that even 50% require catheterization, there are approximately 41,500 U.S. women with IDC resulting from spina bifida.

Parkinson’s – 41,250 U.S. Women

“About 1 million Americans are thought to have Parkinson’s,” of which ~330,000 are women.⁹ “20% to 30% of women with Parkinson-related syndromes will have urodynamic findings of detrusor hypocontractility or areflexia.”¹⁰ (25% of 330,000 = 82,500.) Assuming the detrusor hypocontractility or areflexia in 50% of these women is severe enough to require use of urinary catheters, then there are ~41,250 U.S. women with Parkinson’s-related IDC.

Multiple System Atrophy (MSA) – 36,274 U.S. Women

“Prevalence rates (for MSA) show 4-5 cases per 100,000 persons.”¹¹ The current U.S. census shows 163,233,090,000 women → $163,233.09 / 4.5 = 36,274$ U.S. women with MSA, virtually all of whom require catheterization. Importantly, “Neurogenic urinary retention can be a major cause of morbidity in multiple-system atrophy.”¹²

Spinal Cord Injury (SCI) – 14,100 U.S. Women

~ 282,000 people in the U.S. live with a spinal cord injury (SCI), with males accounting for approximately 80% of SCI cases.¹³ This means there are an estimated 56,400 U.S. women with SCI. The percentage of these women requiring catheterization is not known; however, the vast majority have voiding dysfunctions.¹⁴ Assuming $\frac{1}{4}$ of all U.S. women with SCI require catheterization, then there are approximately 14,100 U.S. women with IDC resulting from SCI.

All Other Neurologic Conditions – 40,000 U.S. Women

Other neurologic conditions resulting in IDC include cauda equina syndrome, iatrogenic injury (usually due to over-use of anticholinergics or pelvic surgery), dementia and even IDC diagnosed as idiopathic as neurologic involvement can be difficult to document. As the aggregate number of U.S. women with IDC resulting from these conditions is not known, a low percentage of the U.S. female population ($163,233,090,000 \times 0.00025$) was applied, resulting in an estimated 40,000 U.S. women.

⁵ Bradley WE (1980) *Diagnosis of urinary bladder dysfunction in diabetes mellitus*. Ann Intern Med 92:323–326

⁶ Nanigian DK, Keegan KA, Stone AR. (2007). Diabetic cystopathy. *Current Bladder Dysfunction Reports*, 2(4), 197-202.

⁷ Kaplan SA, Te AE, Blaivas JG. (1995) *Urodynamic findings in patients with diabetic cystopathy*. J. Urol. 153, 342–34410.

⁸ National Institute of Neurological Disorders and Stroke (NINDS). (2013) *Spina Bifida Fact Sheet*. NIH Publication No. 13-309

⁹ Parkinson’s Foundation (2018) *Statistics*. Accessed Feb 17, 2018.

¹⁰ McCrery RJ, Appell RA. (2005) *Female neurogenic vesicourethral dysfunction: evaluation and management*. *Curr Urol Rep*. 6(5):348-55.

¹¹ Vanacore N, Bonifati V, Fabbrini G, et al. (2001) *Epidemiology of multiple system atrophy* *Neurol Sci*. 22: 97.

<https://doi.org/10.1007/s100720170064>

¹² Ito T, Sakakibara R, Yasuda K, et al. (2006) *Incomplete emptying and urinary retention in multiple-system atrophy: When does it occur and how do we manage it?* 21(6):816-23

¹³ National Spinal Cord Injury Statistical Center, *Facts and Figures at a Glance*. (2016) Birmingham, AL: University of Alabama at Birmingham. <https://www.nscisc.uab.edu/Public/Facts%202016.pdf>

¹⁴ *Bladder Management for Adults with Spinal Cord Injury: A Clinical Practice Guideline for Health-Care Providers*. (2006). The Journal of Spinal Cord Medicine, 29(5), 527–573

1.3 Clinical

1.3.1 Major Adverse Health Outcomes Associated with Medical Condition

IDC is itself a serious medical problem and complications include urinary retention, overflow incontinence, recurrent UTIs (sometimes progressing to sepsis), bladder stones and impaired renal function.

1.4 Unmet Need

1.4.1 Description of Unmet Need

Due to its neurologic origin, IDC is generally incurable and there are few clinical options. While new procedures (notably the Medtronic InterStim® and Allergan Botox®) provide alternatives for neurogenic *overactive* bladder, none have emerged for neurogenic *underactive* bladder, i.e. IDC. The vast majority of women with IDC must use urinary catheters for bladder drainage.

Urinary catheters may be the most commonly used of all medical devices; however, with chronic use they routinely cause serious problems, notably: 1) urinary tract infections (UTIs), 2) low quality of life (QoL), and 3) encrustation. These problems are acutely heightened for women with IDC, since they must use urinary catheters every day for the rest of their lives.

Reducing catheter-associated urinary tract infection (CA-UTI) is widely recognized by CMS and others as one of the highest health priorities:

“A long term indwelling catheter (>2 to 4 weeks) increases the chances of having a symptomatic UTI and urosepsis. The incidence of bacteremia is 40 times greater in individuals with a long term indwelling catheter than in those without one.” - CMS Manual System Pub. 100-07 State Operations Provider Certification

In addition, for women with IDC, any review of their clinical options is a reminder of their psychological as well as medical circumstances. Despite the very serious nature of their primary medical conditions (stroke, MS, spina bifida, SCI, etc.), most will tell you that the inability to void normally is the most bothersome part of their daily lives. That is because this ability is basic to our sense of independence from the time we are small children. To lose this control has important psychological consequences. Many who lose it as adults view it as demarcating event, signaling the end of their normal adult lives and the start of dependency.

1.4.2 How the inFlow Addresses Unmet Need

As a urinary prosthesis, the inFlow’s clinical objectives are to: 1) provide a safer, more convenient and more dignified alternative to chronic use of urinary catheters and 2) to restore as much voiding function as possible to women with neurologically impaired bladders.

The inFlow urinary prosthesis is a system with two components:

1. “inFlow device” – a sterile, single-use urethral insert in a biocompatible silicone housing, packaged with a disposable introducer (**Figure 1**).
2. Activator – a hand-held remote control required to operate the internal valve-pump mechanism in the inFlow device. The Activator comes with a Base Station for recharging its internal battery (**Figure 2**).

Prior to initial device insertion, the inFlow Sizing Device, a sterile single-use device with transient patient contact, is used to determine the appropriate device length. The inFlow Sizing Device consists of a 7cm inFlow housing/spacer with gradients corresponding to urethral length and a solid ABS piece in place of the valve-pump mechanism. A second, adjustable tab is moved until it touches the meatus to determine device length (**Figure 3**).

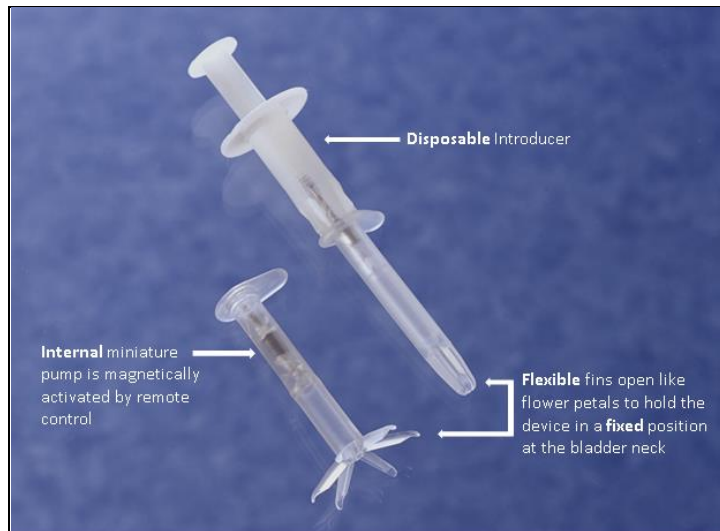


Figure 1. The inFlow device



Figure 2. Activator in its Base Station



Figure 3. inFlow Sizing Device

The inFlow device is a 3-7cm long device in a silicone housing. A physician performs device sizing and initial insertion. Device insertion is similar to that for a urinary catheter (**Figure 4a**). The inserted device resides almost entirely in the urethra (**Figure 4b**) so that only the user knows it is there. As with an indwelling (Foley) catheter, the inFlow device should be removed and replaced every 29 days. The device can be easily and safely removed by simply grasping its tab and pulling straight out (**Figure 4c**). Insertion of replacement devices can often be performed by a trained caregiver or spouse.

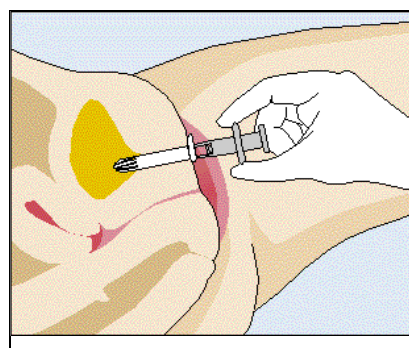


Figure 4a. Device insertion

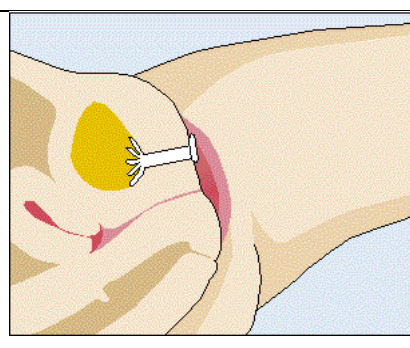


Figure 4b. Device *in vivo*

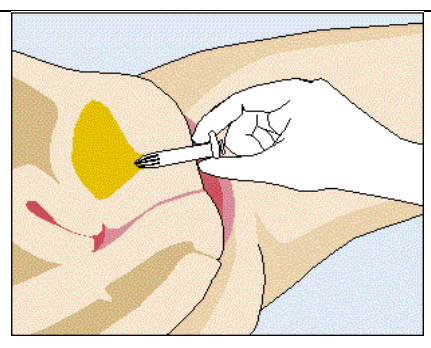


Figure 4c. Device removal

Voiding with the inFlow urinary prosthesis mimics normal urination, as shown in **Figure 5**:

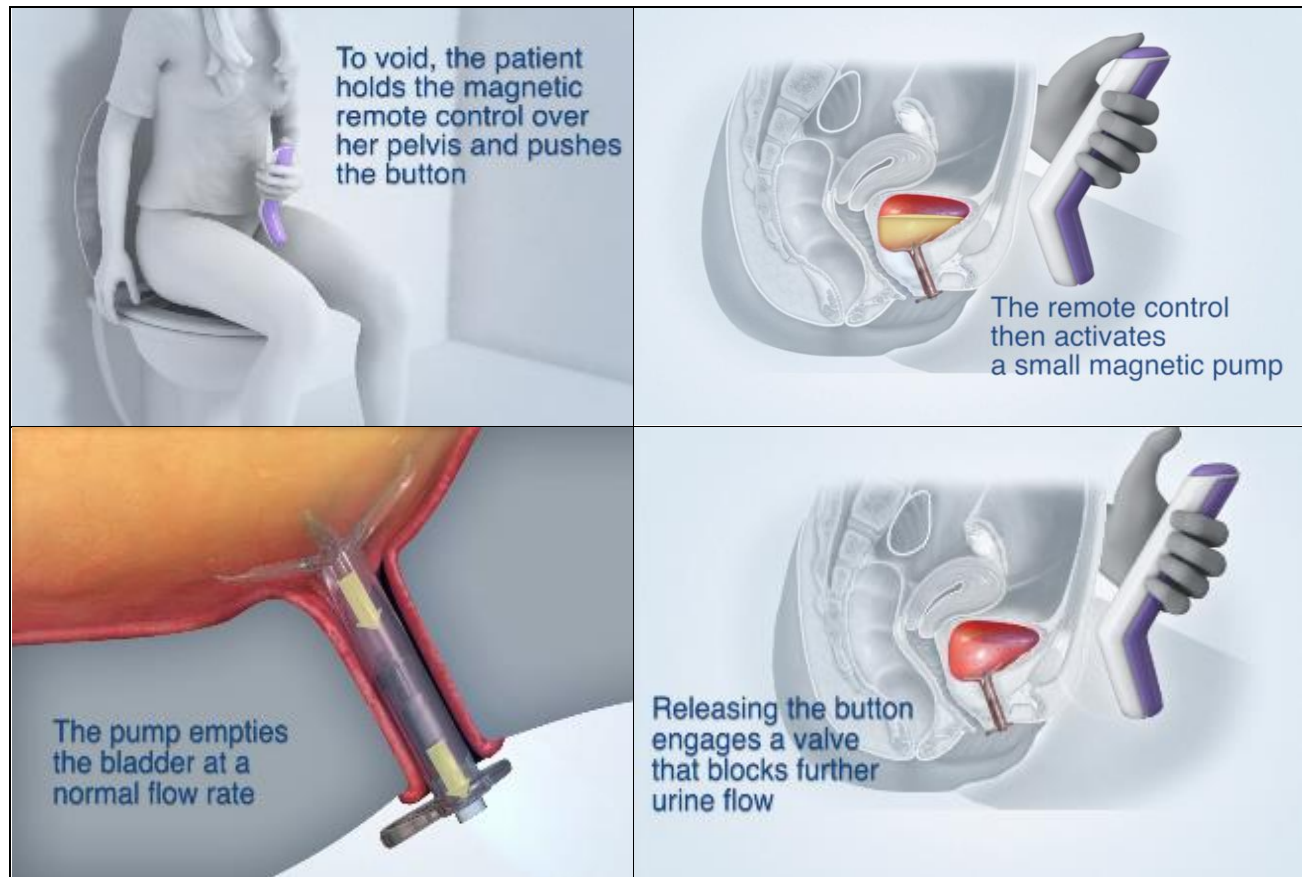


Figure 5. Voiding with the inFlow Urinary Prosthesis

1.4.3 Indicated Patients

The inFlow Urinary Prosthesis is intended for a very specific population, women with IDC as determined via urodynamics findings, multiple bladder volume measurements showing a clinically significant post-void residual (>75cc) or a history of urinary catheterization.

1.4.4 Fit in Clinical Pathway

Importantly, the inFlow Urinary Prosthesis can be used by patients using either intermittent or indwelling urinary catheters and so should be offered to all indicated patients.

The inFlow can improve quality of life for any women using urinary catheters, but is of particular value to those using indwelling (Foley) catheters. Many women with IDC either cannot or will not perform self-catheterization, making CIC impractical. Due to their serious and often debilitating primary medical conditions, many women with IDC lack the dexterity or visual acuity to perform this procedure. Others, particularly women of a certain age and those who have been sexually abused, may be unwilling to repeatedly touch their genital area. If a woman cannot or will not use CIC, then she is likely to end up with a Foley catheter and urine drainage bag, despite the low quality of life and high rate of UTIs that invariably result:

- UTIs from Foley catheters cause over 13,000 deaths and add \$1.85 Billion in direct medical costs annually in U.S. hospitals alone. (CDC figures for 2002, the most recent year with published data)

Many of these patients can use the inFlow; however, and it can provide them with a level of safety and effectiveness equal to or superior to that of CIC. In addition, clinical studies show that the inFlow can improve quality of life by as much as 80% for CIC users.

2 Product Information

2.1 Technology Description and Characteristics

The inFlow Urinary Prosthesis represents the current state of the art in bladder drainage, as evidenced by its pivotal trial, which showed it to have greater infection resistance and improved quality of life as compared to clean intermittent catheterization (CIC), the current standard of care.

The inFlow Urinary Prosthesis utilizes a unique magnetic coupling/transfer technology that is fully described in U.S. Patent Numbers 5,762,599 and 9,839,373, and to the best of Vesiflo’s knowledge no similar device exists. The inFlow’s pivotal trial compared it to CIC because urinary catheters are the only medical alternatives for emptying the bladder and CIC is the current standard of care. As shown in **Table 5**, although the inFlow and CIC both provide bladder drainage, their clinical objectives, use of technology and mechanisms of action differ substantially:

	inFlow Urinary Prosthesis	Urinary Catheters
Clinical Objective	Restore/normalize voiding function to the greatest extent possible	Empty bladder
Technology Used	Magnetic coupling	None (tube)
Mechanism of Action	Actively pumps urine from bladder	Passively drains urine from bladder

Table 5. Comparison of Bladder Drainage Methods

Confirmation of the inFlow’s novelty was recently provided by the following regulatory agencies:

- In August 2016, when the GMDN Agency determined that no similar devices existed in their database and issued a new GMDN code and term, 62305 Intraurethral Valve-Pump.
- In October 2014, when the FDA approved the inFlow as a De Novo device, i.e. one with no predicate, establishing the inFlow as a new product type, as described in **Table 6**.

2.2 Device Classification and Approval Status

The inFlow urinary prosthesis has a 20-year history as a CE-marked device and is classified by the International Standards Organization (ISO) as a Class IIb device.

In the U.S., the inFlow was considered a Class III device and was required to conduct a pivotal trial in support of a PMA (premarket approval) application. After review of the favorable safety data from the pivotal trial and other clinical studies; however, the FDA down-classified the inFlow to Class II. The inFlow received FDA approval number DEN130044 via the De Novo pathway on October 14, 2014, establishing a new FDA product type. The inFlow’s FDA regulatory classification, which is shown in **Table 6**, was published in the U.S. Code of Federal Regulations (CFR) on April 6, 2015:

Regulation Number	Classification Code	Description
876.5140	PIH	Device: Urethral Insert with pump for Bladder Drainage Definition: The device is intended to empty urine from the bladder under patient control. Physical State: A catheter-like device with internal pump mechanism that is placed in the urethra. Technical Method: Under patient control, the internal pump inside the urethral insert draws urine out of the bladder when voiding is desired, and blocks urine flow when continence is desired. Target Area: The device is placed in the urethra.

Table 6. inFlow FDA Regulatory Classification

In 2016, the inFlow was approved for use in Korea. In addition to evidence submitted for FDA approval, the Korean FDA required new animal-based biocompatibility testing per the most recent ISO standards, including ISO 10993-10:2013 Skin Sensitization Testing and Subacute Toxicity Testing (4-week implantation).

2.3 Procedure Codes

Diagnosis: ICD-10-CM R33.9 – *Retention of urine, unspecified* is typically used. All patient medical record documentation should appropriately reflect medical justification and necessity, including documentation of permanent disability.

	Initial Device Insertion	Replacement Device Performed in Office	Replacement Device Performed at Home
Code	CPT® 53899, <i>Other Procedures on the Urethra</i> , to include charges for urethral measurement, device insertion, patient education, bladder filling and confirmation of patient ability to void with device	CPT® 53899, to include charges for device insertion and device	HCPCS A4335 for device only (no physician services)
Payment Reference Crosswalk Example	CPT 53855, <i>Insertion of a temporary prostatic urethral stent, including urethral measurement</i> , which describes the procedure for a physician-inserted urethral device and has similar work and practice expense RVUs as those associated with the inFlow device and services	CPT® 53855-52 (include explanation of reduced services)	N/A

Table 7. inFlow U.S. Procedure Codes

Please refer to Section 4.2 Possible Coding for more information.

2.4 Device Components and Specifications

This report applies to the following items:

Product Name	Model Number	Manufacturer
inFlow Intraurethral Valve-Pump	203511-XX*	Vesiflo, Inc.
Activator	403507-X2	Vesiflo, Inc.
inFlow Sizing Device	203511-SD	Vesiflo, Inc.

*XX denotes device size. Nine (9) lengths are available, from 3.0-7.0cm

Table 8. inFlow FDA Device Components

The inFlow Intraurethral Valve-Pump (the “inFlow device”) is a urethral insert containing an internal valve and pump. The device diameter is 24Fr and nine (9) device lengths are available in order to suit individual patient anatomy, ranging from 3 to 7 cm (in 0.5 cm increments). The only patient-contacting material is medical-grade silicone and devices are sterilized via gamma radiation. Individual devices are packaged in Tyvek along with a disposable introducer and are replaced every 29 days.

The Activator is a hand-held control unit that operates the inFlow device. The Activator is battery-powered and contains a large magnet in a sealed, moisture resistant ABS housing. Only one Activator is required for each patient and based on the anticipated life of its rechargeable lithium battery should last for at least three (3) years.

A second accessory, the inFlow Sizing Device, is a sterile single-use device with transient patient contact that is used to determine the appropriate device length.



Figure 6. The inFlow Intraurethral Valve-Pump and Activator

3 Value Evidence Supporting TECHNOLOGY

Extensive data from a variety of sources exists regarding the inFlow's safety and effectiveness. Please refer to **Exhibit A** for a listing of animal studies and laboratory testing. The results of seven (7) clinical studies are summarized in the next section (3.1). *The inFlow also has a 20-year history of device use, exceeding 1,250 women-years in clinical experience.*

No serious or long-lasting adverse events associated with inFlow use have been reported.

3.1 Clinical Efficacy and Patient Outcomes

A total of seven clinical studies (total $n=385$) concerning the inFlow have been published in major peer-reviewed journals, including the inFlow's pivotal trial ($n=157$) and six investigator-sponsored studies (total $n=228$), three of which were long-term studies of 1-4 years. The results of those studies are summarized in the next two sections (3.1.1 and 3.1.2).

3.1.1 Pivotal Trial, A Comparison to the Present Standard of Care

The FDA classified the inFlow as a Class III device. This classification is usually limited to surgical implants and similar devices; however, the agency was concerned about the potential for reflux, autonomic dysreflexia and urosepsis and so required a pivotal trial and other Class III-level evidence in support of a PMA (premarket approval) application. An 18-site, single-arm crossover study ($n=157$) was conducted under IDE G970029 to compare safety, effectiveness, and patient satisfaction of the inFlow Urinary Prosthesis versus clean intermittent catheterization ("CIC"), the current standard of care for long-term bladder drainage. The study was limited to females with a urodynamically confirmed diagnosis of atonic bladder (now "impaired detrusor contractility" or IDC) who were successfully using CIC.

As a high dropout rate was anticipated, the prospective goal was to enroll 274 subjects to yield an evaluable sample size of 123 subjects. Also, documentation for all study metrics was maintained on dropouts as well as continued users. This allowed retrospective comparisons between these groups, which found no survivor bias and verified the integrity of study findings.

115 subjects were considered evaluable for the primary endpoint. The subject flowchart is shown in the following table:

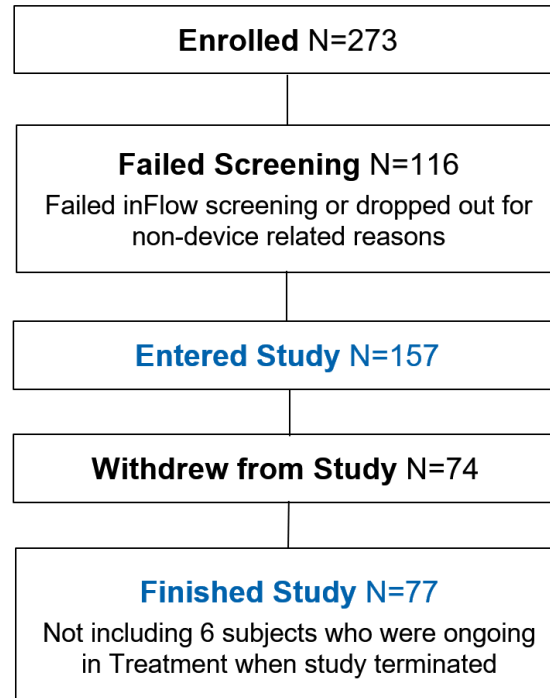


Table 9. Subject Flowchart for Pivotal Trial

The pivotal study protocol was quite robust in that it not only compared the inFlow to the current standard of care, it did so using (only) a cohort for whom the standard of care was their usual method of bladder drainage, in many cases for as long as 20 years. A randomized trial could not be conducted as it was not practical to create an indistinguishable comparator arm. It should be noted; however, that the crossover design that was employed has certain benefits:

1. Because they capitalize on the subject as her own control, crossover trials require substantially fewer subjects than more traditional two group designs, providing similar data (with a smaller sample size) to a two-arm study of twice the size.
2. True randomization can be difficult to achieve, particularly in less than large-scale studies. A crossover study minimizes the contribution of variability in subject disease state and response to treatment as these are controlled within the same subject.

The study design in the inFlow’s pivotal trial featured the subject as her own control by incorporating two study phases with objective measurement of the primary and secondary endpoints during both phases. Furthermore, because the standard treatment in the baseline phase of this study was CIC and the subjects’ usual mode of treatment, there was little likelihood for carryover effect possible such as is seen in studies of, for example, two different drug treatments.

In Phase One, Baseline data was collected by monitoring CIC use for 8 weeks. In Phase Two, subjects were crossed over to Treatment by monitoring inFlow use for 16 weeks. At the final treatment visit, the inFlow device was not replaced and the subject resumed CIC for a 4-week period. Upon the completion of this period, the subject returned for a final visit at which a measurement of the primary clinical endpoint was obtained after CIC. The subject was then offered the option to continue inFlow device use in an open enrollment period.

Clinically appropriate endpoints were selected for this study:

1. Primary Endpoint: Post-void residual (PVR or the amount of urine remaining in the bladder after device use). The dichotomous variable was a comparison of PVR values. PVRs were considered to be "comparable" under the protocol if the values for both CIC and the inFlow were less than 50cc, or if the CIC PVR was greater than 50cc and the inFlow PVR was less than or equal to the CIC PVR. The goal was to have at least 95% of subjects with comparable PVRs.
2. Secondary Endpoint: Quality of Life (QOL) as measured on a 100-point scale by the Wagner I-QOL, a validated continence-specific instrument. The goal was to show equivalence.
3. Safety: Comparative rates of urinary tract infection (UTI) and other adverse events.

All study endpoints were evaluated using standardized protocols throughout both phases of the study. For the primary endpoint, the same technicians performed catheterization for PVR determination following a standard protocol throughout both phases of the study.

As shown in the following table, the results of the pivotal study were positive and unambiguous:

	Prospective Measures	N	CIC	inFlow	Design Objective	Result
Primary Endpoint	Percent Subjects with comparable PVR between CIC baseline and on inFlow treatment	115	NA	98% (113/115)	95% comparability rate with a 95% confidence interval half-width of $\pm 4\%$	Passed - 98% comp. PVRs; Clopper-Pearson 95% CI 94%, 99.8%
Secondary Endpoint	Quality-of-life per 100pt scale	85	42.2	67.4	Equivalence	Superior - $p < 0.0001$
Safety	UTI rate per subject month. (Other AEs discussed below.)	77	0.12	0.10	Equivalence	Passed

Table 10. Summary of inFlow Pivotal Trial Results

1. **Primary Endpoint: Post-void residual (PVR).** All subjects with PVR data available for both Baseline and Treatment were considered evaluable. This resulted in a total of 115 evaluable subjects, including some dropouts. Almost 100% of subjects met the primary endpoint. 98% (113/115) of evaluable subjects had a median inFlow Treatment PVR that was no greater than the median CIC Baseline PVR or both medians were < 50 cc, with median PVR at each visit during inFlow Treatment ranging from 10-20cc. (1-sided exact 95% confidence lower limit: 95%; 2-sided exact 95% confidence interval 94% - 99.8%). 92-98% of all subjects had comparable PVRs at every treatment visit.

These results successfully met the protocol stated goal of demonstrating a 95% comparable rate with a 95% confidence interval half-width of approximately $\pm 4\%$. There was no significant difference in baseline PVR volume between those included in and excluded from the analysis of the primary endpoint ($p=0.54$ by stratified logrank test).

As shown in the following table, the within subject inFlow vs. CIC difference indicated a statistically significant lower PVR on the inFlow ($p=0.02$):

PVR Volumes	N	Median
Baseline (CIC)	115	13cc
Treatment (inFlow)	115	10cc

Table 11. Comparison of Within Subject PVR Results

Viewed in clinical perspective, both the inFlow and CIC were highly effective, with median values well below the 50-100cc level considered acceptable voiding function.

2. **Secondary endpoint: Quality of life (QOL).** This analysis was performed on the evaluable subjects who had both Baseline and Treatment QOL data per the Wagner I-QOL ($n=85$). The mean score at Baseline was 42.2, which increased to 67.4. This 25-point improvement ($p<0.0001$) while using the inFlow is both clinically and clinically significant for this 100-point scale, and represents nearly a 60% improvement. The median percent improvement from Baseline was 54%.

There was no statistically significant difference in mean Baseline score between those included vs. excluded in QOL analysis (42.2 vs. 45.8: $p=0.30$ by linear regression). In any case, QOL is arguably important only to those who continue to use the device.

3. **Safety: Rate of Urinary Tract Infection (UTI).** Per subject-month rates for subjects completing the study declined with continued inFlow use (Baseline=0.12, first half of Treatment period=0.11 and second half of Treatment period=0.08). This analysis was performed with completers only ($n=77$) in order to compare event rates during different study periods with the same set of subjects; however, the UTI experience in this study is based on 417 patient-months cumulative exposure in 157 patients. Thus, the UTI rate observed is a representative and robust estimate of what might be expected in clinical use and this finding is notable in that no *indwelling* bladder drainage device has ever been shown to have the same UTI rate as *intermittent* catheters.

Note: The Investigational Plan for the pivotal trial conducted under IDE G970029 defined UTIs as marked by presentation of clinical symptoms and confirmed by urine analysis (and so is consistent with current CDC recommendations). AB was also tracked as a leading indicator, although high bacteria counts do not necessarily lead to UTI.

Safety: Other Adverse Events. No serious or long-lasting adverse events associated with inFlow use were reported in the pivotal trial. Indwelling (Foley) catheters contact patients 24/7 and are known to have a high rate of adverse events, including infection, encrustation, leakage, discomfort, and bladder spasm. As an indwelling device, it was anticipated that adverse events associated with inFlow use would be more frequent and severe than those for CIC, which contacts subjects for only minutes per day. There were no significant differences in event rates between the CIC Baseline and inFlow Treatment periods; however, except for hematuria, genitourinary pain, bladder inflammation, and urinary incontinence. All hematuria events were of mild or moderate severity and none required treatment or device removal. All bladder inflammation events were mild in severity. All genitourinary pain and incontinence events were mild to moderate in severity. Of note, no inFlow device failed due to encrustation. Discomfort and leakage increased during inFlow Treatment and although all cases were mild in severity, this caused numerous subjects to discontinue device use, most within 1-4 days. Since discomfort and leakage are clinically minor events and since post-analysis showed that the safety profiles for subjects who withdrew from the study did not differ significantly from those who completed the study, device acceptance does not appear to be related to safety. The issue of device acceptance is discussed in the next section.

Importantly with regard to all study findings, actual device exposure time far exceeded prospective goals (2928 weeks vs. 1220 weeks).

Device Acceptance: Results were consistent with the prospective estimate that ~50% of subjects would fail to complete the study for device-related reasons. This estimate was based on both clinical experience with the inFlow and the reported acceptance rates for other similar devices.

Discomfort and leakage increased during inFlow Treatment and although all cases were mild in severity, this caused numerous subjects to discontinue device use. Discomfort, more accurately device awareness, and leakage are not responses unique to the inFlow. Both are frequently reported in patients using indwelling urinary catheters (and unlike the inFlow, their use is rarely elective).

Neither the pivotal trial nor any other published study of the inFlow (total $n=385$) could identify a reliable predictor of device success based on demographics or pathology. As previously noted however, most of the subjects in the pivotal trial who discontinued device use did so in the first 1-4 days and the pivotal trial did show that an on-device trial was effective in identifying appropriate candidates and did no harm to those who chose not to continue with device use.

Chronic voiding disorders are known to be difficult-to-treat and most interventions for them have historically had limited success. As more fully described in **Exhibit B**, FDA-prepared Summary of Safety and Effectiveness (SSED) reports of acceptance rates in the pivotal trials for other currently covered devices for chronic voiding disorders were similar to that for the inFlow:

- The device acceptance rate for the Rochester Medical FemSoft® intraurethral insert for stress urinary incontinence (SUI) was 45.33% of 150 subjects who entered the 12-month study (22.7% of 300 subjects screened) and the UTI rate was high.
- Of 157 subjects who were implanted with the Medtronic InterStim® for neurogenic OAB, only 27.39% completed the 12-month study (9.4% of the 458 screened) and surgical complications were frequent.

Although the most recent studies of the Medtronic InterStim report success rate >60%, it took time and clinical experience (now over 250,000 procedures) to develop clinical protocols to increase device acceptance rates. Likewise, there has been a learning curve concerning best practice with the inFlow, which is also a new type of device.

Following the pivotal study, Lynch et al. showed that device acceptance can be increased by providing pre-insertion patient education and post-insertion nursing support. In their one-year study ($n=20$), only one subject discontinued device use for reasons related to the device. Although inFlow was initially described by its inventors as a urinary prosthesis, Lynch et al were the first clinicians to account for the fact that, like most other prosthetic devices, it requires a period of accommodation and adjustment to work well for many patients. Following a rehab-type protocol, they started by setting appropriate patient expectations prior to initial device insertion, i.e. disclosing the risk of discomfort and leakage, but also explaining that any problems were likely to be temporary and unlikely to do harm. Post-insertion, they provided nursing support to closely monitor any problems or concerns, make small adjustments and “coach” patients through the accommodation period.

The Lynch protocol is in marked contrast to the one employed in the pivotal trial, where “implantation” of the device was treated as similar to a surgical procedure and discomfort and leakage were considered to be adverse events warranting dismissal of subjects from the study. Rather, discomfort and leakage are more appropriately viewed in clinical context. They are clinically minor events and while unfortunate, should not be viewed as akin to a surgical complication. Discomfort, leakage and all other adverse events were quickly resolved by device removal, which can be easily and safely done at any time, even by patients. Also, since the inFlow is a non-surgical device, its use does not preclude any subsequent clinical options. Pivotal subjects who withdrew from the study simply resumed use of CIC, their previous method of bladder drainage.

Bottom line, device acceptance is hard to predict, but the pivotal showed it is easy to test for with an on-device trial and Lynch showed it can be increased with patient education and nursing support.

Recent clinical use in the U.S. has continued progress in more effectively managing the transition from bladder drainage with urinary catheters to normalizing urination with the inFlow, including new protocols for the use of Botox for MS patients. Also, as described in **Section 4** of this document, Vesiflo plans to implement a device-based mHealth condition management system that is expected to inform improved methods for device acceptance and continuing care of women with IDC.

Safety Profile: The FDA considered the safety data from the inFlow’s pivotal trial to be compelling enough to change its device classification from Class III to Class II and approve it via the De Novo pathway.

Safety	No serious or lasting adverse events associated with inFlow use were reported.
	The rate of UTIs was less than that for clean intermittent catheterization, the current standard of care and per subject-month rates for subjects completing the study <u>declined</u> with continued inFlow use (Baseline=0.12, first half of Treatment period=0.11 and second half of Treatment period=0.08). This finding is notable in that no <i>indwelling</i> bladder drainage device has ever been shown to have the same UTI rate as <i>intermittent</i> catheters.
	The 2928 weeks of device exposure in the pivotal study were considerably greater than the 1220 weeks that had been prospectively agreed to.
	Despite a higher rate of subject withdrawals than anticipated (non-device related), there are no “missing data.” The subjects who passed the one-week screening and continued to use the device were followed to assess the primary endpoints. Safety data were recorded for subjects who dropped out.
	With regard to survivor bias, the safety profiles of the subjects who dropped out do not differ in any clinically significant way from those who completed the study. Also, safety data are largely relevant only for those who continue to use the inFlow device, since unlike a pharmaceutical, it has no active agent that continues to affect subjects after they are exposed to it.
	There were no adverse tissue changes; the device does not alter the anatomy.
	No device failed due to encrustation.
	There were no significant differences in event rates between the CIC Baseline and inFlow Treatment periods, except for hematuria, genitourinary pain, bladder inflammation and incontinence. All hematuria events were of mild or moderate severity and none required treatment or device removal. All bladder inflammation events were mild in severity. All genitourinary pain and incontinence events were mild to moderate in severity.
	The device can be easily and safely removed at any time, even by patients. Subjects who discontinued use simply resumed use of CIC, their previous method of bladder drainage.
Effectiveness	Primary Endpoint-PVR: 98% (113/115) of evaluable subjects met this endpoint. (1-sided exact 95% confidence lower limit: 95%; 2-sided exact 95% confidence interval 94-99.8%)
	Secondary Endpoint-QOL: The inFlow significantly improved quality of life compared to the current standard of care. Among those subjects with both Baseline and Treatment QOL data ($n=85$), patient scores for the Wagner I-QOL (100-point scale) increased by a mean of 25 points ($p<0.0001$) while using the inFlow. The median percent improvement was 54%. The results were both statistically and clinically significant.
	97.4% (75/77) of the subjects who completed the Treatment phase opted-in to continue using the inFlow afterward.

Table 12. Summary of Safety and Effectiveness per the inFlow’s Pivotal Trial

A preliminary report of the inFlow’s pivotal study was published by two Clinical Investigators, Drs. Tu and Kennelly; however, the FDA’s De Novo Report is the preferred public report of the pivotal trial as it is their review of the company’s FDA submission, which was based on finalized SAS files and the more definitive analyses they allowed:

- Chen TYH, Ponsot Y, Carmel M, Bouffard N, Kennelly MJ, Tu LM. *Multi-Centre Study of Intraurethral Valve-Pump Catheter in Women with a Hypotonic or Acontractile Bladder*. Eur Urol 2005; 48: 628–633 (**Attachment 2**)
- FDA Center for Devices and Radiological Health, *DEN130044_Vesiflo_inFlow_de_novo_summary*. Oct 2014 (**Attachment 2**)

3.1.2 Non-Comparative Clinical Studies

In addition to the inFlow's pivotal trial, six investigator-sponsored clinical studies (total $n=228$) have been published in major peer-reviewed journals (**Attachment 2**):

1. Mazouni C; Karsenty G; Bladou F; Serment G: *Urethral device in women with chronic urinary retention: an alternative to self-catheterization?* Eur J Obstet Gynecol Reprod Biol 2004; 115(1): 80-84
2. Lynch WJ, Testa GA, Bell D: *A Study to Determine Subjective and Objective Benefits of a Remote-Controlled Intra-Urethral Device for the Management of Female Acontractile Bladder.* Brit J Urol 2003; 92: 960-963.
3. Madjar S, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *Long-term follow-up of the inFlow™ intraurethral insert for the treatment of women with voiding dysfunction.* Eur Urol 2000; 38:161-166.
4. Madjar S, Sabo E, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *A remote controlled intraurethral insert for artificial voiding - A new concept for treating women with voiding dysfunction.* J Urol 1999; 161:895-898.
5. Schurch S, Suter S, Dubs M: *Intraurethral sphincter prosthesis to treat hyporeflexic bladders in women – Does it work?* Brit J Urol 1999; 84:789-794.
6. Nativ O, Moskovitz B, Issaq E, Condrea A, Kastin A, Halachmi S, Burbara J, Madjar S, Beyar M: *A new intraurethral sphincter prosthesis with a self-contained urinary pump.* ASAIO J 1997; 43:197-203.

It is somewhat unusual to have a number of non-company sponsored studies for a proprietary device, which speaks both to the novelty of the device and the acute need that exists in the population it serves. It is worth noting that despite the lack of standardization that inevitably results when studies are conducted by independent investigators all over the world, consistent conclusions under these circumstances are likely to be a better predictor of clinical practice than a series of studies controlled by a single company.

Three studies followed subjects for 1-4 years. These long-term studies are summarized in the following sections.

Lynch et al

In a one-year study of 20 acontractile (IDC) bladder patients that was conducted after the U.S. pivotal study (although it was published before that study was), Lynch et al. reported 80% improvement in quality of life and no negative tissue changes. This study also reported a high rate of device acceptance; only one patient discontinued device use for reasons related to the device.

The following is excerpted from the published report of this study:

“Specific objectives were to show effective and complete bladder drainage and to evaluate any effect that the device has on the quality of life of the patients in the study. Twenty women were recruited for this study (mean age 64.5 years, range 37–87). All patients had no evidence of effective detrusor contraction during urodynamic assessment.

All patients had used the standard bladder drainage techniques; most had tried more than one of the alternatives. At the time of enrolment the techniques used were ISC in five, indwelling urethral catheter in eight and suprapubic catheterization in seven. All patients had expressed dissatisfaction with their particular method of bladder drainage, and were thus enrolled in this study.

The mean (range) flow rate was 10.7 (9–16) mL/s and the PVR 3 (0–17) mL. Two patients had a single UTI after the initial insertion of the Inflow; these responded to standard antibiotic therapy and did not recur. The patient who had had recurrent UTIs before inserting the Inflow interestingly had no further infections after establishing adequate bladder drainage.

The present small study shows that patients felt they had a significant improvement in their QoL when using the Inflow to effect their bladder drainage. If provided with appropriate support while the catheter was established even the mentally impaired can achieve effective and adequate bladder emptying. The side-effect profile is low and the risk of infection seems minimal.”

Lynch et al. showed that a high rate of device acceptance can be achieved by providing pre-insertion patient education and post-insertion nursing support, specifically by:

- Pre-insertion: Setting appropriate patient expectations by disclosing the risk of discomfort, but also explaining that any discomfort was likely to be temporary and unlikely to do harm.
- Post-insertion: Providing nursing support to closely monitor any problems or concerns, make small adjustments and “coach” patients through the accommodation period.

Madjar et al

Madjar reported a long-term study in two parts. Subjects were 16 to 88 years old (mean age 56) with urinary retention due to “difficulty voiding.” The study was conducted at several centers in Germany and one center in Israel. This study demonstrated similar results to the pivotal study with respect to bladder emptying (post-void residual), complications, reasons for withdrawal and UTI rates.

In the first part ($n=92$), 45 subjects discontinued device use <7 days due to discomfort or leakage and 47 subjects were followed with a mean follow-up time of 7.6 months, range 2-26 (total 357 subject-months). In the second part, 21 subjects (Israel only) were followed for more than a year with a mean follow-up time of 24.6 months, range 12-44 months (total 517 subject-months).

Causes of voiding dysfunction included previous pelvic surgery and external radiation ($n=11$), multiple sclerosis ($n=9$), diabetes ($n=7$), spinal injury ($n=6$), but was unknown in most cases ($n=59$). Unlike the pivotal trial, in which 99% of subjects were CIC users, this study included subjects whose previous treatments included indwelling catheter ($n=21$) and no treatment ($n=16$), as well as CIC ($n=55$).

All subjects received the inFlow device at the start of the study. Subjects returned for month follow-up, including urinalysis and culture, symptom assessment, satisfaction questionnaire and uroflow. The device was removed within 4 months (mean 7.1 days) in 45 cases (49%), due to local discomfort ($n=25$), urinary leakage ($n=14$), and difficulties with operation ($n=6$). The remaining 51% continued to use the device for a mean of 7.6 months. All remained dry and experienced complete bladder emptying. Twenty-two users (47%) had asymptomatic bacteriuria and 14 had a symptomatic urinary tract infection, all of which were successfully treated with oral antibiotics (14 UTIs/357 subject-months = 3.9% incidence).

Women who were sexually active prior to treatment did not have any difficulty with intercourse after treatment. All users were “satisfied” or “very satisfied” with the device and they preferred it to previous treatment modalities. Treatment success was associated with previous CIC, diagnosis of atonic bladder (now IDC), and sexual activity. Treatment failure was associated with no previous treatment for voiding difficulty, unknown etiology of voiding dysfunction, and pre-treatment bacteriuria. By multivariate analysis the only independent predictor of treatment failure was the absence of prior treatment for voiding difficulty.

In the second part of the study, among the 21 subjects who were followed for more than 1 year, 15 (71.4%) developed asymptomatic bacteriuria. Four episodes of symptomatic urinary tract infection were recorded, of them one upper urinary tract infection (4 UTIs/517 subject-months = 0.01% incidence). All patients who continued treatment were satisfied or very satisfied with the device.

Madjar's conclusions were as follows:

"The new remote controlled intraurethral inFlow Catheter is useful for managing difficult voiding in women. The pump and valve assembly mimics normal urination by enabling a good stream of urine with complete bladder evacuation as well as continence between voids. The cost and incidence of symptomatic urinary tract infection are similar to those of clean intermittent catheterization. This device is safe and effective for women with difficult voiding."

Mazouni et al

In a study of 60 subjects with chronic urinary retention, median age of 61.9 years old (range 40–89), Mazouni et al utilized inclusion and exclusion criteria similar to that in the pivotal trial and showed similar results to that study. In sum, Mazouni found the inFlow to be effective in emptying the bladder, had few significant complications and was a good solution for many users, but that a high percentage of subjects discontinued use. The following is excerpted from the published report of this study:

"The mean maximal peak flow measured after 1 month was 14 ml/s (range 7–18). The post-voiding residual (PVR) volume was 15 ml (range 0–40). The incidence of urinary infection was 3.3%. (This compares to) a reported rate of 12% of urinary infection after 5 years of clean intermittent catheterization.

The abandonment of the prosthesis was noted in 50% (30/60) of cases within the first 15 days after implantation. The patient was free to stop treatment at any time. The insert was either removed at the clinic or by the patient herself. At the end of the procedure, 30 patients were using the In-Flow™ prosthesis with successful bladder emptying. The mean duration of the experience was 95 months (range 1–870). The longest experience with the device was 29 months, and in this case, the device has been changed 31 times."

The published report notes that the abandonment rate was affected by both device failures (for reasons long since corrected) and cost and makes two interesting observations:

"The acceptance rate of urethral devices in incontinence is about 56–60% (per published reports), which is similar with our results as 50% of all patients were using the prosthesis at the end of the study. There was no statistically significant difference in patient characteristics that predispose to a success of or withdrawal from the prosthesis."

As has occurred in other long-term studies of the inFlow, the investigators report several cases in which subjects recover voiding function despite a history of IDC and pre-study confirmation of this diagnosis via urodynamics, etc.:

"Spontaneous voiding function among the group of chronic urinary retention occurred without surgery in three cases at 10, 90 and 330 days, respectively, of using the device."

Study conclusions were as follows:

"The In-Flow™ prosthesis is an interesting alternative to classical treatment as it is associated with a low number of adverse effects. The complications were local and essentially caused by mechanical problems. In conclusion, the advantage of this prosthesis is the ease of insertion and removal, its low morbidity and the recovery of autonomy by the patient. This intraurethral prosthesis is an attractive, simple technique for use as an alternative to catheterization."

Summary of Non-Comparative Clinical Studies

All six clinical studies concerned similar populations to the pivotal study and for the most part reported similar findings. No serious or lasting adverse events were reported in any study and conclusions improved steadily over time, as investigators came to more fully understand both the benefits and limitations of this unique device, culminating in the study by Lynch et al, which demonstrated best clinical practice, resulting in a high device acceptance rate.

Key findings from these six studies are summarized in **Table 13**:

PI/Lead Author	Journal	Study Size	UTI Rate*	Key Findings/ Conclusions
Lynch	British Journal of Urology	20	0.01	Lynch reported that 14 evaluable subjects had a total of 2 UTIs in 156 subject-months (0.01% incidence), almost no device-related dropout , 80% quality of life improvement per Wagner I-QOL scores, no negative tissue changes and concluded that <i>"the (inFlow) device provides an effective method of bladder drainage, with few side-effects and significant improvement in QoL."</i>
Mazouni	European Journal of Obstetrics and Gynecology	60	0.03	Mazouni reported that although 30 subjects dropped out <15 days, 30 evaluable subjects had a total of 6 UTIs in 178 subject-months (3.4% incidence) and concluded that inFlow is <i>"An attractive, simple technique for use as an alternative to catheterization."</i>
Madjar	European Urology	21	0.01	Madjar reported that when 21 subjects from his two-part study continued on-device, they had a total of 4 UTIs in 517 subject-months (0.01% incidence) and concluded that, although dropout was a problem (due largely to discomfort), <i>"all patients were satisfied with the device and preferred it to previous treatment modalities used."</i>
Madjar	Journal of Urology - American Urological Association	92	0.04	Madjar reported that in the first phase of his two-part study, 47 subjects had a total of 14 UTIs in 357 subject-months (3.9% incidence) and all resolved with oral antibiotics.
Schurch	British Journal of Urology	18	Not Reported	Early study suffered from poor transition of a new technology to clinical practice and product quality issues.
Nativ	American Society for Artificial Internal Organs	17	0.03	Nativ reported that 14 evaluable subjects had a total of 3 UTIs in 118 subject-months (0.025% incidence). Interestingly, 2 subjects recovered bladder function after prolonged inFlow use (as did 8 subjects in other studies, total 10/228=4.4%) .
Totals/Average		228	0.02**	207 unique subjects (Madjar studies were continuous for same cohort)

* UTI rate was not a prospective measure in the studies cited. This table is based on a retrospective analysis of studies reporting UTI rates.

** The five studies reporting UTI rates reported a total of 29 UTIs in 1,326 subject-months.

Table 13. Summary of Findings from Investigator-Sponsored inFlow Studies

All studies reporting UTIs reported low rates. Importantly, Madjar’s two-part study reported that the UTI rate declined with continued device use (from 3.9% to 1% incidence), a finding consistent with the UTI trend reported in the pivotal trial. Of interest, several studies reported subjects who recovered normal bladder function after 6-12 months of having their voiding normalized with inFlow use.

3.2 Core Value Drivers

Its clinical studies showed the inFlow Urinary Prosthesis to have superior performance in critical areas where urinary catheters are known to be deficient, specifically:

1. Urinary tract infections (UTIs),
2. Quality of life (QoL), and
3. Encrustation.

These problems are acutely heightened women with impaired detrusor contractility (IDC) of neurologic origin, since their bladder function has been permanently impaired by their neurologic disease or injury (MS, spinal cord injury, stroke, spina bifida, etc.) and they must use urinary catheters on a life-long basis to prevent the occurrence of urinary retention and its attendant complications and to prevent episodes of overflow incontinence.ⁱ

The present standard of care for women with IDC is clean intermittent catheterization (CIC) and the most common alternative is indwelling (Foley) catheters. Long-term use of CIC appears to result in fewer complications, such as infections and bladder and renal stones, than does chronic indwelling catheter use.^{ii,iii,iv,v,vi,vii}

The following three sections compare the performance of these urinary catheters to that of the inFlow with regard to the most serious catheter-associated problems.

3.2.1 Urinary Tract Infections (UTIs)

The inFlow's low rate of UTIs is its most significant therapeutic distinction. The inFlow's pivotal trial showed it to have a lower rate of UTIs than clean intermittent catheterization (CIC), the current standard of care. This was a significant enough finding that the FDA put out a news release when it approved the inFlow and its Chief Scientist for devices, Dr. Maisel, made the following statement:

"It is noteworthy that the most significant of adverse events – UTI – appears to occur at a lower rate with the inFlow device as compared to CIC." –FDA 10-14-2014 News Release^{viii}

Importantly, the inFlow can also be used not only by women who use CIC, but also by those who use indwelling (Foley) catheters, which are known to have an exceedingly high rate of UTIs. These women are at significant risk of life-threatening (and expensive) infection:

- Women who use Foley catheters on a chronic basis suffer multiple UTIs annually.
- In at least 5% of these women, a UTI will progress to urosepsis.
- As many as 40% of those women will die as a result.

UTIs from urinary catheters are quite common, but their full impact is not well understood, even by most healthcare providers.^{ix} Per CDC estimates, catheter-related UTIs cause over 13,000 deaths and add \$1.85 billion in direct medical costs annually in US hospitals alone.^x These estimates are notable for their limited scope: a) they include only patients with indwelling catheters; b) they do not include community-dwelling catheter users or those in assisted living or long-term care facilities; and c) they are based on the most recent year with completed data, but that year is 2002.

In a worrisome trend, the risk from catheter-associated UTIs is increasing with the emergence of resistant bacteria, while attempts to improve the infection resistance of urinary catheters with bactericidal coatings, etc. have been only modestly if at all successful.^{xi,xii} As a result, it is likely that UTI-related mortality has increased or will increase.^{xiii} Clearly, the best (and most cost effective) treatment for infection is prevention.

Its 18-site ($n=157$) pivotal trial showed the inFlow to have superior infection resistance to the current standard of care. The inFlow's pivotal trial was a LOE Ib study conducted under IDE that compared not only the safety and effectiveness, but also the user experience of the inFlow device versus CIC, the current standard of care for long-term bladder drainage. This study utilized a crossover design in which each subject served as her own control and was limited to women with a urodynamically confirmed diagnosis of atonic bladder (IDC) who were successfully using CIC (some for as long as 20 years). Subjects' CIC use was monitored for eight weeks to establish a Baseline and then they were crossed over to 16 weeks of inFlow Treatment. Findings concerning UTI rates were as follows:

UTI rates for the inFlow started off slightly lower than for CIC and *declined* with continued use (CIC Baseline=0.12, first half of InFlow Treatment period=0.11 and second half of inFlow Treatment period=0.08).

The UTI experience in this study is based on 417 patient-months of cumulative exposure in 157 patients; thus, the UTI rate observed is a representative and robust estimate of what is expected in clinical use.^{xiv} This finding is consistent with those from all long-term studies conducted by independent investigators. Mazouni reporting only 3% UTI incidence and Madjar reporting 3.9% of subject months with UTI in 357 months of device use and all resolved with oral antibiotics.

The inFlow's infection resistance is thought to result primarily from its ability to mimic normal voiding behavior by providing periodic, forceful, and complete evacuation of urine.

In contrast, a Foley catheter does none of these things. Both the inFlow device and CIC maintain the normal urine fill-void cycle, which in turn preserves bladder tone, and both effectively empty the bladder; however, only the inFlow provides turbulent evacuation of the urine, maintaining the flush mechanism that the body normally uses to protect itself against bacterial buildup. Also, the inFlow is a sterile device that is inserted only once per month, whereas CIC requires 4-6 insertions daily, each of which is an opportunity to introduce bacteria. Finally, the inFlow device is inserted using a sterile introducer and, after insertion, is almost entirely contained within the urethra, minimizing hand contact and other opportunities to introduce bacteria.

3.2.2 Quality of Life (QoL)

Most users regard the inFlow's ability to improve quality of life as its greatest benefit. Its pivotal trial showed that the inFlow improved QoL by almost 60% compared to CIC, the current standard of care,^{xv} and an investigator-sponsored one-year study showed that it improved QoL by 80%.^{xvi}

Chronic catheterization can be psychologically devastating. Either patients are literally tied to a bag of their own urine, which many regard (correctly or not) as an end-stage development, or they must self-catheterize, a procedure that is so burdensome its long-term compliance is low.

As previously noted, the present standard of care for women with IDC is CIC; however, since CIC requires a tube to be inserted into the bladder 4-6 times per day, it is only practical if a woman can self-catheterize. Unfortunately, many women with IDC either cannot or will not self-catheterize. Many lack the visual, manual, or cognitive ability to safely perform this procedure due to age and/or their primary medical condition. Others choose not to. Many women, particularly the elderly and the sexually abused, are reluctant to repeatedly touch their genital area. If a woman cannot or will not use CIC, then she is likely to end up with a Foley catheter and urine drainage bag, despite the high rate of UTIs and low quality of life that invariably result.

For women with IDC, any review of their clinical options is a reminder of their psychological as well as medical circumstances. Despite the very serious nature of their primary medical conditions, most will state that the inability to void normally is the most bothersome part of their daily lives, as this ability is basic to a sense of independence from the time we are small children. To lose this control has important psychological consequences. Many who lose it as adults view it as a demarcating event, signaling the end of their normal adult lives and the start of dependency. As crucial as it is, women with IDC currently have almost no hope of regaining the ability to void normally.

As a prosthetic device, the inFlow's clinical objective is to normalize voiding to the greatest degree possible. This results in tangible benefits that are meaningful to its users, including:

- a) eliminating the need to self-catheterize multiple times daily;
- b) eliminating tubes and bags, improving body image and hygiene;
- c) allowing most users to void without assistance, increasing self-reliance; and
- d) allowing use of a toilet, a psychologically significant benefit as that is the "normal" way to void.

3.2.3 Encrustation

Encrustation is perhaps the most commonly encountered clinical problem with indwelling urinary catheters, and about 50% of all patients with indwelling catheters experience problems with blockage due to encrustation. This is distressing to patients and can result in urine leakage around the catheter, urinary retention, and pain on removing of the catheter, a procedure that can also result in urethral trauma.^{xvii}



Figure 7. Indwelling catheter with encrustation

This problem has proven quite difficult to resolve:

“In an attempt to avoid the development of encrustation, various measures have been tried, including the use of long-acting antimicrobial coatings, and treatments designed to detach biofilms as they form. Currently however, these measures are far from perfected, and encrustation will remain a significant problem for indwelling catheters for the foreseeable future.”^{xviii}

A study by D. Stickler of the Microbiology Research Group at Cardiff University in the UK (described in Exhibit A) showed the inFlow’s encrustation resistance to be at least 8.4 times better than a silicone Foley catheter, the current gold standard:^{xix}

*“Under conditions that simulated a heavy infection of *P. mirabilis*, where a conventional Foley catheter blocked with crystalline biofilm after 25.7 hours, the inFlow device drained the bladder for at least 9 days... (and its) central lumen appeared to be essentially clear.”*



Figure 8a. The inFlow device during study, shown in place in the outlet of bladder model



Figure 8b. The inFlow device post-study, showing minimal encrustation and a clear central lumen after 9 days of draining bacteria-saturated urine substitute

In addition, there was no encrustation reported in the inFlow’s pivotal trial.

The inFlow’s encrustation resistance is thought to result primarily from its ability to provide turbulent evacuation of the urine, maintaining the flush mechanism that the body normally uses to protect itself against bacterial buildup.

3.3 Quality of Life Outcomes

3.3.1 Core Value Drivers

The evidence supporting the inFlow’s ability to improve quality of life (QoL) by restoring functional capacity and personal dignity is described in Section 3.2.2; however, QoL is an issue that is often better described by the patients themselves.

The Videos page of Vesiflo’s Web site (www.vesiflo.com/videos) has four (4) videos that give voice to patient experiences with the inFlow, including one of a patient and her caregiver/ spouse testifying in support of inFlow coverage at the June 16, 2016 HCPCS DME Public Meeting:



“My wife no longer suffers from the indignity of her husband having to catheterize her multiple times per day. We love inFlow” – Testifying Patient’s Caregiver/ Spouse

The inFlow’s value in improving the QoL of its users has been documented by numerous letters from patients and their families. The following quotes are representative:

“(The inFlow is) an unqualified success. It is difficult to put into words the effect it has had on (my daughter’s) life.” - Patient’s Father

“It can simply, yet absolutely transform the quality of lives.” - Patient’s Brother

Physician experts have been equally positive in describing the inFlow’s ability to improve patient quality of life:

“The inFlow device is truly remarkable in its ability to virtually restore the functional behavior of the urinary bladder. No other product, drug, or device can accomplish this to the same degree. The device should be given a high priority consideration for all female patients having difficulty emptying their bladders.”

- Richard Schmidt, MD, inFlow Clinical Investigator and Co-inventor of Medtronic Interstim®

3.3.2 Role of TECHNOLOGY in Improving Patient Quality of Life

Evidence supporting the inFlow's ability to improve patient quality of life (QoL) can be found in sections 3.2.2 and 3.3.1, but is also described in the following patient case histories:

Patient CP. had complications several years after cancer surgery and became unable to completely empty her bladder on her own. At first, she thought that like many women she was experiencing Overactive Bladder symptoms. Eventually, her bladder problems became so troublesome that she visited her local hospital where they discovered that Carolyn, who actually had an Underactive Bladder, had developed hydronephrosis and was becoming uroseptic. After her discharge, Carolyn's urologist recommended she try using the inFlow Urinary Prosthesis in order to completely empty her bladder on a routine basis. Carolyn has now been "on device" for 18 months and has experienced only one minor UTI and there has been no evidence of hydronephrosis.

Patient SA. was diagnosed with Multiple System Atrophy (MSA), which caused her to be unable to empty her bladder. Susan was spending hours in the rest room, but had the constant sensation of being "full" and did not want to leave the house. Her MSA also caused Susan to be unable to abduct her legs adequately, which made it almost impossible for her to be catheterized intermittently on a daily basis. Normally, this would mean that she would have to rely on a Foley or suprapubic catheter, but Susan's urologist felt it worth attempting the use of the inFlow Urinary Prosthesis to empty her bladder more completely and therefore address her chronic UTIs. After 14 months of device use, Susan no longer suffers chronic UTI's and she is maintaining a healthy timed toileting interval with the assistance of her care givers. She now enjoys attending plays, watching her grandchildren play sports and gathering with her family.

3.3.3 Device Safety Profile

The inFlow has demonstrated an excellent safety profile:

- Clinically minor adverse events are routine with all methods of bladder drainage; however, no serious or long-lasting adverse events associated with inFlow use have been reported.
- With regard to one of the most serious adverse events associated with bladder drainage, the inFlow's pivotal trial ($n=157$) showed it to have a lower rate of urinary tract infections (UTIs) than the current standard of care.

Positive safety data from the inFlow's pivotal trial and other sources of evidence were the primary determinant in the FDA's decision to down-classify the inFlow from Class III to a Class II device.

Summary: Impaired detrusor contractility (IDC) is an incurable condition wherein patients cannot generate bladder pressure and so cannot urinate spontaneously. There are currently poor solutions for women with IDC:

- Foley catheterization has a high rate of infection and is psychologically damaging.
- CIC is not suited to many women as self-catheterization requires high levels of cognitive, visual and manual function. Also, even patients who are able to perform CIC often choose not to, as it can be a time-consuming, malodorous procedure that must be performed 4-6+ times per day (120-240x per month). Finally, even those women who can and will perform self-catheterization are in need of improved quality of life.

The inFlow is of high benefit with low risk for those who can use it and per **Exhibit C**, the probable benefit to health from the use of the device outweighs any probable injury or illness from such use.

4 Future Directions and Applications

4.1 Emerging Clinical Applications

Vesiflo plans a two-phase implementation of a mHealth system for the care of women with IDC. Its goal is to provide better overall management of community-dwelling patients, including by identifying potential health issues as early as possible

Phase One - Remote Monitoring: The single most important metric for bladder health (and an important one for general health) is urine output. As shown in **Figure 9**, the inFlow Activator can determine the approximate urine output each time it is used and transmit those data to an aggregating point in the cloud where they can be monitored and alerts initiated when appropriate:

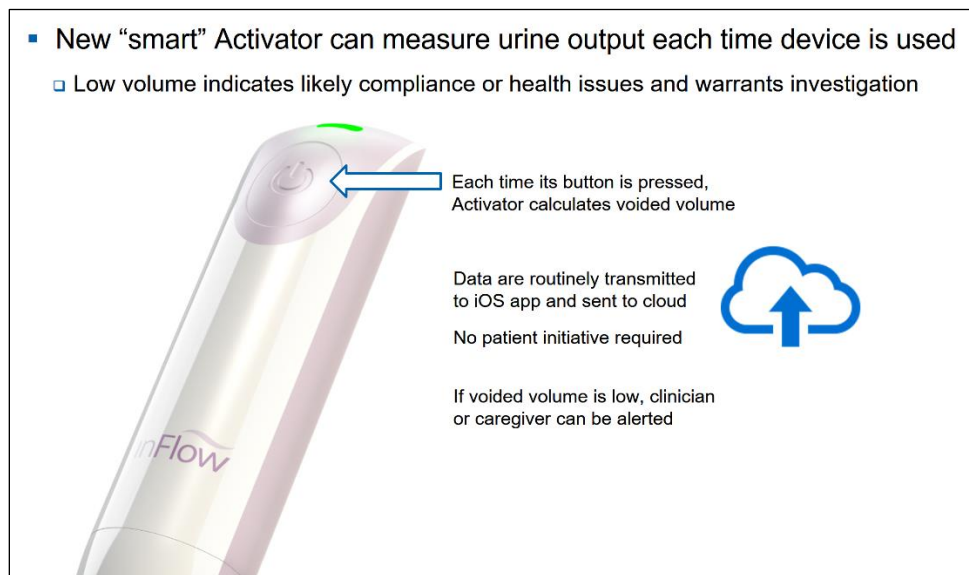


Figure 9. Compliance Data Collection and Transmission

Phase Two – Condition Management: As shown in **Figure 10**, when fully implemented this system will include clinical guidance to inform patient-specific care plans and a patient program for voiding schedules, hydration goals and other recommended behaviors:

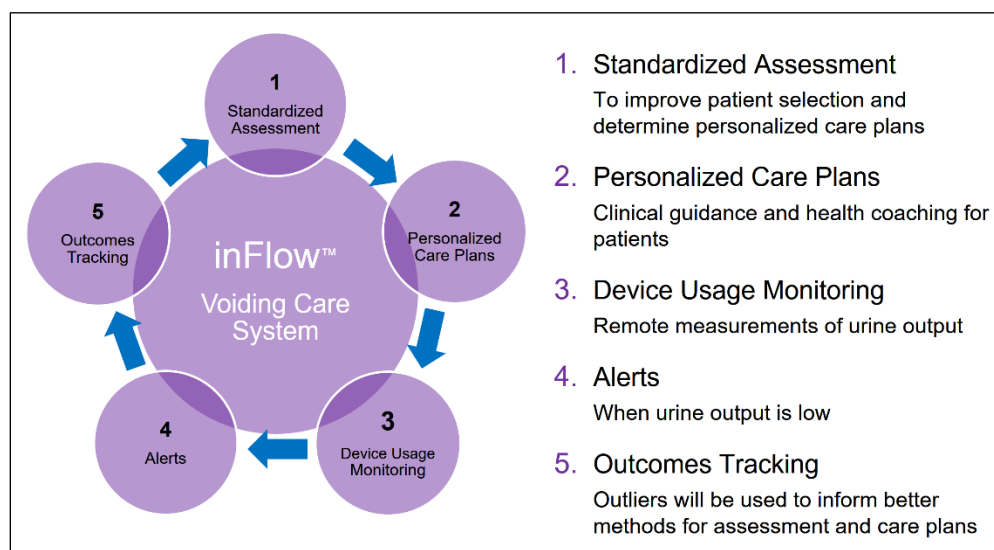


Figure 10. Overview of IDC Condition Management System

References Cited in Section 3.2

- i Bowen LW. *Voiding Dysfunction*. Ob and Gyn Clinics of N Amer 16: 869-882 (1989).
- ii Timoney AG, Shaw PJR. Urological Outcome in Female Patients with Spinal Cord Injury: The Effectiveness of Intermittent Catheterisation. *Paraplegia* 28: 556-563 (1990).
- iii Joiner E, Lindan R. Experience with self intermittent catheterization for women with neurological dysfunctions of the bladder. *Paraplegia* 20:147-153 (1982).
- iv Bakke A. Physical and Psychological Complications in Patients treated with Clean Intermittent Catheterization. *Scand J Urol Nephrol Suppl* 150: 1-69 (1993).
- v Tenney JH, Warren JW. Bacteriuria in Women with Long-Term Catheters: Paired Comparison of Indwelling and Replacement Catheters. *J Infectious Diseases* 157: 199-202 (1988).
- vi Vaidyanathan S, Rao MS, Saleem A, Subudhi CL, Rajendran LJ, Shrikhande VV. Fatal intra-peritoneal bladder rupture due to blocked catheter in a paraplegic. *Paraplegia* 17: 272-277 (1979).
- vii Webb RJ, Lawson AL, et al. Clean intermittent self-catheterization in 172 adults. *Br J Urol* 65: 2023 (1990)
- viii FDA News Release "FDA permits marketing of urinary prosthesis device for women." Oct 14, 2014
- ix Saint S, Kowalski CP, Kaufman SR, Hofer TP, Kauffman CA, Olmsted RN, Forman J, Banaszak-Holl J, Damschroder L, Krein SL. *Preventing Hospital-Acquired Urinary Tract Infection in the United States: A National Study*. Clinical Infectious Diseases 2008; 26:243-250
- x Klevens RM, Edwards JR, Richards CL, Horan TC, Gaynes RP, Pollock DA, Denise M. Cardo DM. *Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002*. Public Health Reports; March–April 2007; 122:160-166.
- xi Stickler, D. *Comment re: Types of urethral catheters for management of short-term voiding problems in hospitalized adults*. Neurourology and Urodynamics, 27: 748. doi: 10.1002/nau.20647 (2008)
- xii Centers for Disease Control and Prevention (CDC). *Guideline for Prevention of Catheter-Associated Urinary Tract Infections 2009*. <http://www.cdc.gov/hicpac/pdf/CAUTI/CAUTIguideline2009final.pdf>
- xiii Johnson JR, Kuskowski MA, Wilt TJ. *Systematic review: Antimicrobial urinary catheters to prevent catheter-associated urinary tract infection in hospitalized patients*. Ann Intern Med 2006; 144(2):116-126
- xiv FDA DEN130044 Vesiflo inFlow *de novo* Summary
- xv Vesiflo Direct *De Novo* Petition: inFlow™ Intraurethral Valve-Pump. October 22, 2013
- xvi Lynch WJ, Testa GA, Bell D: *A Study to Determine Subjective and Objective Benefits of a Remote-Controlled Intra-Urethral Device for the Management of Female Acontractile Bladder*. Brit J Urol 2003; 92: 960-963.
- xvii Getliffe K. *Managing recurrent urinary catheter encrustation*. Br J Community Nurs 2002; 7:574,576, 578-580.
- xviii Webber R. *Advances in Urinary Catheter Technology*. Urology News. May 2003.
- xix Stickler D. *Operation of inflow in Proteus mirabilis infected in vitro bladder models*. Unpublished. Conducted at Microbiology Research Group, Cardiff University, UK. 2004.

inFlow Clinical Publications

1. Chancellor M: *Chapter 10, Advanced Technology*. The Underactive Bladder. Springer 2016; 155-161. <http://www.springer.com/us/book/9783319236865>
2. Connolly K, *Reinventing Bladder Drainage, The inFlow™ Urinary Prosthesis for Women and Guardian™ VCS* presentation to the 2nd International Congress on Underactive Bladder. Dec 2015: <http://www.underactivebladder.org/index.php/for-professionals/scientific-presentations>
3. FDA Center for Devices and Radiological Health, *DEN130044_Vesiflo_inFlow_de_novo_summary*. Oct 2014. http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130044.pdf
4. Chen TYH, Ponsot Y, Carmel M, Bouffard N, Kennelly MJ, Tu LM. *Multi-Centre Study of Intraurethral Valve-Pump Catheter in Women with a Hypotonic or Acontractile Bladder*. Eur Urol 2005; 48: 628–633.
5. Mazouni C; Karsenty G; Bladou F; Serment G. *Urethral device in women with chronic urinary retention: an alternative to self-catheterization?* Eur J Obstet Gynecol Reprod Biol 2004; 115(1): 80-84
6. Lynch WJ, Testa GA, Bell D: *A Study to Determine Subjective and Objective Benefits of a Remote-Controlled Intra-Urethral Device for the Management of Female Acontractile Bladder*. Brit J Urol 2003; 92: 960-963.
7. Madjar S, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *Long-term follow-up of the inFlow™ intraurethral insert for the treatment of women with voiding dysfunction*. Eur Urol 2000; 38:161-166.
8. Madjar S, Sabo E, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *A remote controlled intraurethral insert for artificial voiding - A new concept for treating women with voiding dysfunction*. J Urol 1999; 161:895-898.
9. Schurch S, Suter S, Dubs M: *Intraurethral sphincter prosthesis to treat hyporeflexic bladders in women – Does it work?* Brit J Urol 1999; 84:789-794.
10. Nativ O, Moskovitz B, Issaq E, Condrea A, Kastin A, Halachmi S, Burbara J, Madjar S, Beyar M: *A new intraurethral sphincter prosthesis with a self-contained urinary pump*. ASAIO J 1997; 43:197-203.

Exhibits

A. inFlow Animal Studies and Laboratory Testing	28
B. Comparison of Approved Devices for Chronic Bladder Management	32
C. inFlow Risk/Benefit Analysis	37

Attachments

1. inFlow Instructions for Use
2. inFlow Clinical Publications

Exhibit A - Animal Studies and Laboratory Testing

Comprehensive animal and laboratory testing of the inFlow device and Activator has been conducted, as summarized in **Table A**:

Table A. List of Animal Studies and Laboratory Testing

Test Type	Tests Made
Biocompatibility	<p>A variety of animal studies and laboratory tests confirm that the inFlow meets current ISO 10993-1:2009 (Biological Evaluation of Medical Devices) standards for a permanent surface device with mucosal membrane contact. The following biocompatibility tests were performed on final, sterilized samples:</p> <ul style="list-style-type: none"> • ISO 10993-5 Cytotoxicity • ISO 10993-10 Sensitization • ISO 10993-10 Irritation • ISO 10993-3 Genotoxicity • ISO 10993-6 Implantation (for both 13 weeks and 26 weeks) <p>In addition, the following tests were performed re the systemic toxicity of device materials:</p> <ul style="list-style-type: none"> • Chemical analysis of nonvolatile leachables from the silicone elastomer • Biocompatibility testing on the internal magnet assembly: Cytotoxicity, Intracutaneous reactivity and Acute systemic toxicity • Corrosion testing of the internal magnet assembly <p>FDA: "The results of testing support the biocompatibility of the inFlow device for its intended use."</p> <p>Post-FDA approval, new animal-based biocompatibility tests were conducted in Korea to confirm conformance to the most current ISO standards:</p> <ul style="list-style-type: none"> • ISO 10993-10:2013 Skin Sensitization Testing • Subacute Toxicity Testing (4-week implantation)
Sterilization	ISO 11137-2, Sterilization of Health Care Products - Radiation
Additional Applicable Standards	<p>Bench studies, including the following,* demonstrated that the inFlow device and Activator meet their performance specifications and, where applicable, conform to ISO, ASTM and other recognized standards:</p> <ul style="list-style-type: none"> • Catheter Pull-out Force Testing (as per "Inflated Balloon Response to Traction" test in ASTM F623-89 Standard Performance Specification for Foley Catheters) • Catheter Flow Rate Testing (as per "Flow Rate through Drainage Lumen" test in ASTM F623-89) • Catheter's DC Magnetic Field Levels (Alpen Committee standards) • Activator DC Magnetic Field Testing (Alpen Committee standards) • Activator AC Magnetic Field Testing (IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields for a frequency range of 3 kHz to 20 kHz as determined by device electrical spectrum + DC and harmonics)
Device-Specific Tests	<p>A number of bench studies, including the following, demonstrated that the inFlow device and Activator meet design-related performance specifications:</p> <ul style="list-style-type: none"> • High Pressure Test (seal maintained under 200 cm H₂O bladder pressure) • Catheter Pump and Valve Endurance Test (1140 voiding cycles = 6 months' use) • Activator Endurance Testing (6,931 operating cycles ≥3 years operation) • Activator Drop Testing (50 cm onto hard surface) • Activator Battery Endurance Testing (operated 15 days without requiring recharging)
Encrustation Resistance	<p>An <i>in vitro</i> study by Stickley et al of the Microbiology Research Group at Cardiff University, UK compared encrustation performance under worst-case conditions for an all-silicone Foley catheter (which clogged after 25.7 hours) and the inFlow (which still operated normally after 9 days), at which time testing was discontinued.</p>

* Not a complete list

Operation of inflow in *Proteus mirabilis* infected *in vitro* bladder models
Cardiff University, UK

Introduction

The care of many incontinent elderly and disabled people undergoing long-term bladder catheterisation is complicated by encrustation of their catheters. Crystalline deposits form on the catheter surface and block the flow of urine from the bladder. This can put the health and welfare of the patients under serious threat. The problem is caused by the infection of the catheterised urinary tract by the bacterium *Proteus mirabilis*. This organism has the ability to colonize and spread over the catheter surface and produce alkaline conditions in the urine. Under these conditions crystals of calcium and magnesium phosphate are formed, accumulate on catheter surfaces and block the catheter. We compared the performance of the *inflow* device with that of a conventional Foley catheter in a laboratory model of the bladder that had been infected with *P. mirabilis*.

Method

In vitro glass bladder models (Morris *et al* 1997) were fitted with an all-silicone catheter (Figure 1(a)) or an inflow device (Figure 1(b)). 30 ml of artificial urine (Griffith *et al* 1976) was supplied to each bladder model, which were then subsequently inoculated with 10ml of a log phase culture of *P. mirabilis*. After 1hr the flow of urine into the bladders was initiated at 0.5ml/min. In the bladder model containing the *inflow* the urine was allowed to build up in the bladder for 4hrs before the activator was used to empty the urine from the model. The activator was used in this way up to three times during the day (at

4h intervals). The last activation was at 8pm. The flow of urine into the bladder was then switched to 0.35ml/min and the bladder emptied next at 8am. In the control bladder model containing the silicone catheter, urine was allowed to drain continuously in the usual way and the flow of urine into the bladder maintained at 0.5ml/min.

Results

The control all-silicone catheter blocked with crystalline biofilm at 25.7h. The *inflow* device was still draining urine from the bladder model at 9 days after inoculation with *P. mirabilis* (at which point the experiment was stopped). After removal from the bladder model the *inflow* device was examined for encrustation. While crystal formations were visible on the retention mechanism the central lumen appeared to be essentially clear (Figure 2).

Conclusions

Under conditions that simulated a heavy infection of *P. mirabilis*, where a conventional Foley catheter blocked with crystalline biofilm after 25.7h, the *inflow* device drained the bladder for at least 9 days.

References

- Griffith, D. P., Musher, D. M. and Itin, C. Urease: the primary cause of infection-induced urinary stones. *Invest. Urol.*,13:346,1976.
- Morris, N. S., Stickler, D. J. and Winters, C. Which indwelling urethral catheters resist encrustation by *Proteus mirabilis* biofilms? *Br. J. Urol.*,80:58, 1997.

Figure 1(a)

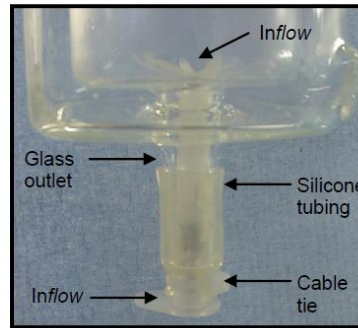
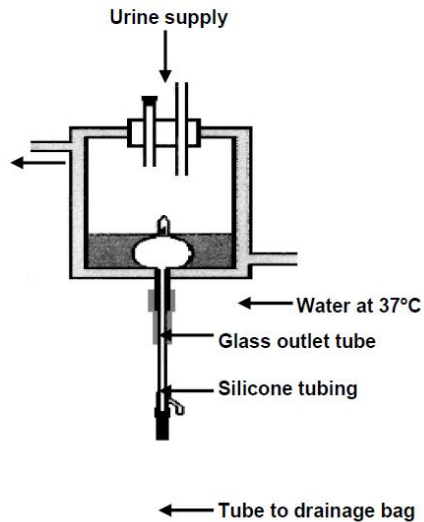


Figure 1(b) top

Figure 1(a) illustrates the *in vitro* laboratory model of the catheterised bladder and its operational set up. The bladder model consists of a glass vessel that is maintained at 37°C by water pumped around an outer jacket by a circulating water bath. A catheter is inserted into the sterile glass bladder through a section of silicone tubing ('urethra') and secured in place by inflation of its balloon. The end of the catheter is then connected to a drainage bag and tube. Urine is supplied to the bladder model via a pump from a reservoir stock held in aspirators ('kidneys'). **Figure 1(b)** shows the *inflow* device inserted into a bladder model. The *inflow* is inserted through a section of silicone tubing and the glass outlet of the *in vitro* model into the bladder chamber. It is then held in place by a cable tie secured around the silicone tubing and the end of the *inflow* device.

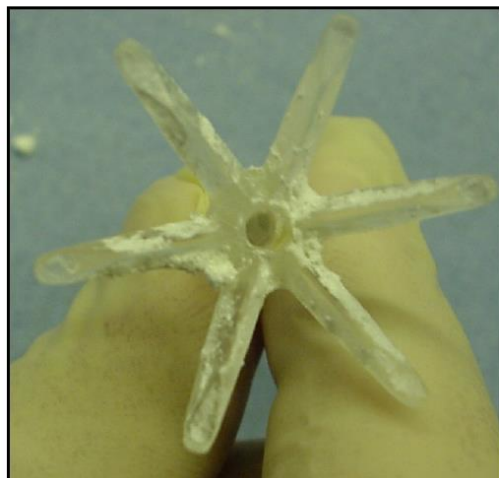


Figure 2 : *Inflow* device removed from the bladder model after 9 days.

Exhibit B – Comparison of Approved Devices for Chronic Bladder Management

Chronic bladder conditions are known to be medically problematic and most interventions for them have historically had limited success. The analysis in this Exhibit was originally submitted to the FDA in support of Vesiflo’s successful De Novo application. It was intended to better inform analyses of the adverse events and device acceptance rate in the inFlow’s pivotal trial and so reviews the pivotal study designs and results for four approved devices, all which are intended to provide some form of chronic bladder management.

This review shows that per SSED (Summary of Safety and Effectiveness Data) reports filed with the FDA, both the adverse events (by type, frequency and severity) and the device acceptance rate in the inFlow’s pivotal trial are consistent with those in the pivotal trials for legally marketed devices for chronic bladder management, including for the following devices currently covered by CMS:

- The device acceptance rate for the Rochester Medical FemSoft® intraurethral insert for stress urinary incontinence (SUI) was 22.7% of 300 subjects screened or 45.33% of 150 subjects who entered the 12-month study (and UTI rate was high).
- Of 157 subjects who were implanted with the Medtronic InterStim® for overactive bladder, only 43 (9.4% of 458 those screened or 27.39% of 157) completed the 12-month study.

Update: Although the most recent studies of InterStim report success rate >60%, it took time and clinical experience (now over 250,000 procedures) to develop protocols to increase device acceptance rates and this remains an expensive (\$20,000+) and highly operator dependent procedure.

A. Opticon Medical Option-vf (K023090)

Indication: Per K023090, “the OPTION-vf is indicated for use only for urinary bladder drainage in female patients: 1) who have acute conditions that require short-term (14 days or less) urinary management; 2) who are capable of operating the device in accordance with its instructions for use; and 3) for whom normal bladder cycling is not contraindicated.” This indication is similar to that for the In-Flow, which also provides controlled bladder drainage and allows normal bladder cycling. The indicated duration of use for the Option-vf (≤14 days) is unique – all other indwelling catheters are indicated for 29 days use, as is the In-Flow device. The restriction to “short-term urinary management” is also unique – no other urinary catheter has an indication for a specific use.

Device Description: The OPTION-vf and the inFlow device have a number of similarities, notably that both contain an integral valve (to allow normal bladder cycling) and both use the same patient-contacting material (silicone).

Clinical Study: Per the 510(k) Summary for K023090, a clinical study was conducted in which subjects “were treated with either a standard Foley indwelling catheter or the experimental Opticon-vF catheter.” A number of specific quality of life improvements are claimed for the Option-vf, but, given the limited detail in the 510(k) Summary, no mention is made of a standardized instrument such as the Wagner I-QOL being used to quantify these improvements.

1. Adverse Events: Per K023090, “a review of adverse events by treatment group showed that adverse event rates were similar between the groups.” By inference it is likely then that the UTI rate for the Option-vf was as high as has been well documented for Foley catheters.
2. Withdrawal Rates: No mention is made in the 510(k) Summary for K023090 of the rate of subject withdrawal in the clinical study.

B. UroMed - Reliance (P960020)

Indication: Per the Summary of Safety and Effectiveness Data (SSED) for P960020, “the Reliance® Urinary Control Insert is intended for use in the management of stress urinary incontinence in adult women.” This indication is essentially the opposite of the inFlow’s, which concerns urinary retention.

Device Description: The Reliance device is physically similar in design to the inFlow device – a rigid cylinder that is sized to the length of the user’s urethra and is held in place by a meatal tab and bladder fixation, in this case a balloon. Insertion and removal are also similar. The Reliance is intended to be removed prior to voiding and a new device inserted post-void.

IDE Study Design: Per P960020, “the clinical study was a multi-center investigation with each patient as her own control. Effectiveness was primarily measured by using a standardized pad weight testing protocol that compared urine loss with the device inserted.” Unlike the inFlow IDE study, the Reliance was not compared to the standard of care.

The target patient population was characterized as follows:

“Since only 36 of the 215 enrolled patients completed the 12-month follow-up, a question was raised as to whether this patient group differed from the large group of patients that withdrew or were unavailable for the test. Analysis of the 12-month group (36 patients) and the larger <12-month group (179 patients) with respect to several baseline characteristics such as age, type of incontinence, pre-device urine loss, hormone replacement therapy, prior UTI history, prior incontinence surgery, mean urine loss before device use, duration of incontinence and age at onset showed no significant differences clinically or demographically between the two groups. The only difference noted was that there were significantly fewer Type-I incontinence patients and more Type-III incontinence patients in the 12-month group. The main reasons for the high rate of patient withdrawals were the clinical protocol requirements, extension of the study from 4 to 12 months and urethral discomfort/irritation associated with the device use.”

1. Adverse Events

Adverse events during treatment phase were very similar to the inFlow, except that Reliance had higher UTI rates.

- Regarding the high UTI rates, the company simply stated that “Based upon the nature of the device, the target population and the adverse events profile as summarized in the preceding adverse event table, the issue of device related UTI, secondary to ascending bacteria, was examined in further detail. Unfortunately, no data exist on the rates of positive culture and UTI in the study cohort prior to entry; therefore, we cannot calculate relative risk with and without the device for this patient population.”
- 78% of patients reported urethral discomfort/irritation as an AE.

2. Withdrawal Rates

- 372 subjects were screened, 71 did not meet eligibility criteria (301 entered study – 80.9% of 372), 86 were not included in the analysis for various reasons including pain and unwillingness to use the device (215 were included in analysis – 57.8% of 372, or 71.4% of 301).
 - Study Exclusions 5 and 6 effectively excluded from analysis patients for whom the device was ineffective. [“The firm also excluded... any patients who met one of the following criteria: (5) patients whose urine loss did not decrease significantly while using the device during the first post-enrollment pad weight study, and (6) patients who experienced four UTIs while using the device. (All data from these patients were included in the safety analysis.)”]

- Of the 215 patients included in the analysis, 123 (33.1% of 372, or 40.86% of 301) continued through the 4-month follow up; only 50 patients (13.4% of 372, or 16.61% of 301) completed the study (12-month follow up). Dropouts included 76 patients (35% of the 215 who were included in the analysis) due to “discomfort” and “unable/unwilling” to use the device.
- Of the 123 patients at 4-month follow up, only 97 were evaluable (26.1% of the 372, or 32.22% of 301); of the 50 completers, only 36 were evaluable (9.7% of the 372, or 11.96% of 301).

Note that CDRH granted expedited review status for the Reliance device, based on the belief that it represented a specific public health benefit for the treatment of female stress urinary incontinence, when compared to existing treatment options. Reliance was approved by the FDA with no known requirement for an additional pre-market study to address deficiencies in described above in safety, dropouts or indications. Per panel recommendations, the only requirements were for a post-approval study [“...an evaluation of the long-term (i.e., 5-year) effects of the device on a minimum of 150 patients (to) assess urethral integrity and provide a detailed analysis of urinary tract infections, including bacteriologic analysis of urinary pathogens.”] and for a change of labeling [“...only for the management of stress urinary incontinence in female patients...”].

C. Rochester Medical - FemSoft (P990002) – COVERED BY CMS

Indication: Per the SSED for P990002, “the FemSoft® Insert is intended for use in the management of stress urinary incontinence in adult women.” This indication is the same as for the Reliance and again the opposite of the In-Flow’s, which concerns bladder drainage.

Device Description: The FemSoft device is a urethral insert similar in function and design to the Reliance, but with differences intended to increase comfort, specifically, a non-rigid cylinder with a lubricous coating. Like the UroMed Reliance, the FemSoft is intended to be removed prior to voiding and a new device inserted post-void.

IDE Study Design: The IDE study for the FemSoft device was very similar in design and outcomes to that for the Reliance, with similar concerns regarding dropout rates and their implications for safety and the identification of target population.

1. Adverse Events

Device-related AEs were similar to Reliance and the inFlow, with again the exception of bacteriuria, symptomatic and asymptomatic UTIs which were very high, similar to Reliance and Foleys and much higher than the inFlow’s:

Event Type	Total No. Events	Total No. Subjects with Event
Bacteriuria >10,000 CFU	70	44 (29.3%)
Symptomatic UTI	51	37 (24.6%)
Asymptomatic UTI	12	10 (6.6%)

2. Withdrawal Rates

300 patients were screened for six weeks prior to device insertion and subject to a variety of voiding-specific evaluations. At the completion of the Screening Period, 150 subjects who met all inclusion and exclusion criteria entered the treatment phase. Only 100 patients continued to 3-month follow up (33.3% of 300, or 66.66% of 150); only 68 completed the study, defined as 12-month follow-up (22.7% of 300, or 45.33% of 150). Almost half of all withdrawals were due to pain/discomfort and other device-related complications.

FemSoft, like Reliance, was approved with the same post-approval study requirement [“...an evaluation of the long-term (i.e., 5-year) effects of the device on a minimum of 150 patients. This post-approval study should assess urethral integrity and provide a detailed analysis of urinary tract infections, including bacteriologic analysis of urinary pathogens.”], based on the panel recommendation.

D. Medtronic – InterStim® (P970004) – COVERED BY CMS

Indication: Per the SSED for P970004, “the Medtronic SNS System (InterStim) is indicated for the treatment of urinary urge incontinence in patients who have failed or could not tolerate more conservative treatments.” Again this is essentially the opposite of the indication for the inFlow, which is concerned with atonic (underactive) bladder versus urge UI (a/k/a overactive bladder).

Device Description: An implantable medical device utilizing sacral nerve neuromodulation. After an initial trial with an external device, the InterStim is permanently implanted

IDE Study Design: The IDE study for the InterStim was very similar in design and outcomes to the Reliance and FemSoft studies, with similar concerns regarding dropout rates and their implications for safety and adequacy of target population.

1-2. Adverse Events and Withdrawal Rates

- Of the 458 patients who underwent on-device screening – only 157 (34%) ended up with an implant (= entering treatment phase).
- Of 157 patients who received implants, 51 (32.5%) had to undergo surgical revision. There were 79 revision surgeries performed, with some patients requiring up to 5 revision surgeries.
- Of the 157 patients who received implants (= entered treatment phase), only 43 (9.4% of 458, or 27.39% of 157) completed the study (12 months), of which only 38 were evaluable (8.3% of 458, or 24.20% of 157).

A large number of post-approval independent, peer-reviewed clinical studies mirror the InterStim IDE study statistics – in terms of screening efficiency, complications (revision surgery) and overall retention rates with the implant. Several recent examples are described below:

- Screening efficiency:
 - In a retrospective review of 1,508 Medicare patients records^{xviii} (a random 5% sample of Medicare InterStim patient records) to evaluate the effectiveness of the screening methods to assess suitability for permanent implantation, only 39.9% of screened patients were found suitable for permanent implantation.
 - In a 92-patient single-center study^{xviii} 50% of screened patients were suitable for permanent implant.
- Long-term implant retention:
 - In an international 17-center study on 163 patients Van-Kerrebroeck *et al*^{xviii} report that of those subjects who passed screening and had InterStim implanted, after 5 years 68% of patients reported urge incontinence; 56% of patients with an indication of urgency frequency and 71% of those with an indication of retention had successful outcomes.
 - In another prospective, controlled, randomized clinical study Weil *et al*^{xviii} report a 32.4% failure rate at 36 months.

- Based on these and other reports, if one multiplies approximately 45% of patients passing the on-device screening by 65% retention rate afterward, **about 29% of the defined target population actually is successful with the treatment.** This is similar to the tolerability rate that the In-Flow showed in its IDE study –overall completion rate was 77/273 = **28.2%**; in the amended protocol 102/173 (59%) passed the on-device screening, and 48% of those (49/102) went on to complete the study – again overall completion rate of **28.3%**.

Update: Although the most recent studies of the InterStim report success rate >60%, it took time and clinical experience (now over 250,000 procedures) to develop clinical protocols to increase device acceptance rates and this remains an expensive (\$20,000+) and very operator dependent procedure.

Summary

- All PMA devices in this review display a similar pattern in their IDE studies:
 - A few hundred patients were screened (300-458) for each study per their respective inclusion and exclusion criteria.
 - A portion of those screened actually enter the treatment phase (34-80.9%).
 - A small percentage of those who enter treatment phase actually complete the study (8.3-22.7% of those screened; 23-45.3% of those entering the treatment phase).

The inFlow IDE study is consistent with this pattern. 273 patients were enrolled/screened, 157 entered the treatment phase (57.5% of 273), 77 completed treatment phase (49% of 157, or 28.2% of 273 – a larger percentage than any other PMA in this group). Importantly, unlike the subjects in the other studies cited, those in the inFlow’s study have serious primary medical conditions (advanced MS, stroke, spinal cord injury, etc.) that limited their ability to meet the demands of an IDE study.

- Furthermore – in many independent post-market studies of InterStim, for example, the average “success rate” among the target patient population is about 29%. The inFlow’s IDE success rate is the same (77 completers out of 273 enrolled = 28.2%).
- InterStim has significantly more severe consequences if it fails – requiring up to 5 revision surgeries per patient, whereas the inFlow can be easily and safely removed at any time. Patients then simply resume their previous voiding technique.
- Both the Reliance and FemSoft had higher UTI rates (similar to Foleys), whereas the inFlow’s are similar to CIC. The difference is about a factor of 10x – an order of magnitude.
- The two PMA intraurethral devices – Reliance and FemSoft – reported high incidence of device-related pain/discomfort: 78% for Reliance (which is a rigid device, similar to InFlow), 30% for FemSoft (which is a soft, gel-filled device). The rate for the inFlow falls in between these two with 44.6% - markedly lower than the 78% reported for Reliance, which is the closest in design.
- It is also worth noting that the two PMA intraurethral devices – Reliance and FemSoft – are indicated for treatment of stress urinary incontinence, a much less severe condition than impaired detrusor contractility (IDC) and also one for which multiple treatment options exist, again unlike IDC. Given the lack of good alternatives for IDC patients, the inFlow presents a compelling solution to a real problem for those who can tolerate it, with no real safety risks for those who do not.

Exhibit C – inFlow Benefit-Risk Analysis

The level of evidence required to determine whether an intervention should be considered a standard medical option is generally based on the following factors: (1) level of risk, (2) benefits provided and (3) level of need.

Surgical procedures and systemic medications typically require the highest level of evidence because of their potential risk. The inFlow Urinary Prosthesis is a replaceable, non-surgical device intended to treat a non-life-threatening condition; however, it was considered by the FDA to be a Class III device and so was required to meet PMA-type standards, including a pivotal trial, supporting clinical studies, animal and laboratory testing to confirm biocompatibility as a permanent implant, etc. There is therefore a considerable body of evidence for the inFlow Urinary Prosthesis and it is sufficient to conclude the following:

1. The level of risk is low.
 - a. No serious or long-lasting adverse events associated with device use have been reported in any of the seven clinical studies (total $n=501$) that have been published in peer-reviewed journals, three of which were long term studies.
 - b. Adverse events that do occur can be remedied by removing the device, which can be easily and safely done, even by patients.
 - c. The inFlow is the first *indwelling* bladder drainage device to show the same (or better) UTI rate as clean *intermittent* catheterization (CIC), the current standard of care.
2. The inFlow can provide meaningful medical and psychosocial benefits to selected patients, as shown by its pivotal trial, which compared it to the current standard of care and found the following:
 - a. an equally high level of effectiveness in emptying the bladder (98% of subjects);
 - b. clinically and statistically significantly improved quality of life scores (~60%); and
 - c. distinct patient preference as shown by the fact that 75/77 (97.4%) of the subjects who completed the treatment phase opted-in to continue using the inFlow afterward.
3. The level of need is high. Impaired detrusor contractility (IDC) is an incurable condition that results in permanent urinary retention and there are virtually no medical options other than urinary catheters, which are associated with a high rate of infection and low quality of life.

[Its body of evidence would appear to be sufficient to justify use of the inFlow Urinary Prosthesis as a standard medical option for women with IDC.](#)

The tables that follow provide a risk/benefit analysis constructed according to the FDA guidance document *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* issued on March 28, 2012 and were originally submitted to the FDA in support of Vesiflo's successful De Novo application.

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	<ul style="list-style-type: none"> - What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit? 	<ul style="list-style-type: none"> - The primary endpoint evaluated was post-void residual (PVR), the measure of how effectively the bladder is emptied. Since emptying the bladder is the purpose of any bladder drainage device, PVR is the most clinically meaningful metric possible. The specific prospective measure was Percent Subjects with comparable PVR between clean intermittent catheterization (CIC) Baseline and on inFlow Treatment. (Per protocol, PVR's on CIC and inFlow devices were considered comparable for a subject if median inFlow Treatment PVR was no greater than median CIC Baseline PVR, or if both were <50 cc.) The design objective was to show a 95% comparability rate with a 95% confidence interval half-width of $\pm 4\%$. - The secondary endpoint was quality of life as evaluated by the Wagner I-QOL, a validated incontinence-specific instrument with a 100 point scale. (Higher scores are better.) The design objective was to show equivalence. - The comparative safety of CIC and the inFlow was also evaluated by type of anticipated adverse events, including rate of urinary tract infection (UTI). (See Risks.) - Patients place high value on all of these benefits as the only current alternatives for bladder drainage, urinary catheters, are known to significantly decrease quality of life. Also, the risk of infection and other complications increases when the bladder is not effectively emptied and UTIs are not only uncomfortable, they can progress to urosepsis, a life-threatening condition.
Magnitude of the benefit(s)	<ul style="list-style-type: none"> - For each primary and secondary endpoint or surrogate endpoints evaluated: - What was the magnitude of each treatment effect? - What scale is used to measure the benefit? - How did the benefit rank on that scale? 	<ul style="list-style-type: none"> - Primary Endpoint-PVR: 98% of evaluable subjects (113/115) met this endpoint (Clopper-Pearson 95% CI 94%, 99.8%), i.e. they had a median inFlow Treatment PVR that was no greater than the median CIC Baseline PVR or both medians were <50 cc, with median PVR at each visit during inFlow Treatment ranging from 10-20cc. 92-98% of all subjects had comparable PVRs at every treatment visit. - Secondary Endpoint-QOL: The inFlow was superior to CIC. On a 100-point scale, patient scores for the Wagner I-QOL increased by a mean of 25 points ($p < 0.0001$) while using the inFlow. The median percent improvement was 54%. The results were both statistically and clinically significant.

<p>Probability of the patient experiencing one or more benefit(s)</p>	<ul style="list-style-type: none"> - Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it? 	<ul style="list-style-type: none"> - The study found that on-device screening was the best predictor of which patients will experience a benefit. - The study found that 61% of subjects who passed the on-device screening also completed the study and so experienced a benefit. - Benefits did not vary across subpopulations. A significant percentage of subjects withdrew from the study due to device awareness/ discomfort and incontinence and so did not experience benefits; however, they could not be prospectively identified on the basis of pathology or demographics. - No variation in public health benefit for different populations was shown. -Study subjects who experienced device benefits valued them, as shown by: a) significantly improved quality of life scores compared to the current standard of care and b) the fact that 97.4% (75/77) of all subjects who completed the Treatment phase of the study opted-in to continue using the inFlow afterward.
<p>Duration of effect(s)</p>	<ul style="list-style-type: none"> - Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients? 	<ul style="list-style-type: none"> - Since 98% of evaluable study subjects met the primary endpoint, that treatment effect (the ability to empty the bladder in a clinically complete manner) is consistent. - As atonic bladder is incurable, the improvements in quality of life compared with the best current alternative are of life-long duration.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
<p>Severity, types, number and rates of harmful events (events and consequences):</p>		
<ul style="list-style-type: none"> - Device-related serious adverse events 	<ul style="list-style-type: none"> - What are the device-related serious adverse events for this product? 	<ul style="list-style-type: none"> - No serious or long-lasting events associated with device use have been reported to date, including from the pivotal study, six independently conducted clinical studies and 1,000+ women-years of use outside the U.S.
<ul style="list-style-type: none"> - Device-related non-serious adverse events 	<ul style="list-style-type: none"> - What are the device-related non-serious adverse events for this product? 	<p>Device-related non-serious adverse events for this product are similar to those for urinary catheters. In comparing the device to the standard of care, there were no significant differences in event rates between CIC Baseline and inFlow Treatment periods except for hematuria, genitourinary pain, bladder inflammation, and urinary incontinence. All hematuria events were of mild or moderate severity and none required treatment or device removal. All bladder inflammation events were mild in severity. All genitourinary pain and incontinence events were mild to moderate in severity. Notably, there were no significant increases in urinary tract infections (UTIs), with rates declining over the course of treatment.</p>
<ul style="list-style-type: none"> -Procedure-related complications 	<ul style="list-style-type: none"> - What other procedure-related complications may a patient be subject to? 	<ul style="list-style-type: none"> -No other procedure-related complications have been reported.

<p>Probability of a harmful event</p>	<ul style="list-style-type: none"> - What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device? 	<p>-Non-serious adverse events are common for urinary catheters and most patients can expect them.</p> <p>- The incidence of the most frequently reported harmful events in the study population is as follows:</p> <table border="1" data-bbox="984 396 1442 871"> <thead> <tr> <th colspan="3" style="text-align: center;">(Pt-Months=417)</th> </tr> <tr> <th style="text-align: left;">Adverse Event</th> <th style="text-align: center;">#Events</th> <th style="text-align: center;">Rate</th> </tr> </thead> <tbody> <tr> <td>Asymptomatic bacteriuria</td> <td style="text-align: center;">56</td> <td style="text-align: center;">0.13</td> </tr> <tr> <td>Bladder inflammation</td> <td style="text-align: center;">9</td> <td style="text-align: center;">0.02</td> </tr> <tr> <td>Frequency, urgency, bladder spasms</td> <td style="text-align: center;">37</td> <td style="text-align: center;">0.09</td> </tr> <tr> <td>Gastrointestinal disorder</td> <td style="text-align: center;">21</td> <td style="text-align: center;">0.05</td> </tr> <tr> <td>Genitourinary pain</td> <td style="text-align: center;">70</td> <td style="text-align: center;">0.17</td> </tr> <tr> <td>Hematuria / scant perineal bleeding</td> <td style="text-align: center;">21</td> <td style="text-align: center;">0.05</td> </tr> <tr> <td>Urinary incontinence</td> <td style="text-align: center;">142</td> <td style="text-align: center;">0.34</td> </tr> <tr> <td>Urinary tract infection (UTI)</td> <td style="text-align: center;">53</td> <td style="text-align: center;">0.13</td> </tr> <tr> <td>Vulvovaginal / periurethral disorders</td> <td style="text-align: center;">28</td> <td style="text-align: center;">0.07</td> </tr> </tbody> </table> <p>- The table above reports the actual incidence rate in the pivotal study and is thought to be typical.</p> <p>- The incidence of harmful events does not vary by subpopulation.</p> <p>- Patients are willing to accept the probable risk of harmful events, given the probable device benefits.</p>	(Pt-Months=417)			Adverse Event	#Events	Rate	Asymptomatic bacteriuria	56	0.13	Bladder inflammation	9	0.02	Frequency, urgency, bladder spasms	37	0.09	Gastrointestinal disorder	21	0.05	Genitourinary pain	70	0.17	Hematuria / scant perineal bleeding	21	0.05	Urinary incontinence	142	0.34	Urinary tract infection (UTI)	53	0.13	Vulvovaginal / periurethral disorders	28	0.07
(Pt-Months=417)																																			
Adverse Event	#Events	Rate																																	
Asymptomatic bacteriuria	56	0.13																																	
Bladder inflammation	9	0.02																																	
Frequency, urgency, bladder spasms	37	0.09																																	
Gastrointestinal disorder	21	0.05																																	
Genitourinary pain	70	0.17																																	
Hematuria / scant perineal bleeding	21	0.05																																	
Urinary incontinence	142	0.34																																	
Urinary tract infection (UTI)	53	0.13																																	
Vulvovaginal / periurethral disorders	28	0.07																																	
<p>Duration of harmful events</p>	<ul style="list-style-type: none"> - How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event? 	<p>-Few of the adverse events in the table above required treatment or device removal. Urgency and discomfort resolved shortly after device removal.</p> <p>-All adverse events were reversible.</p> <p>-Except for UTIs, which are resolved by a course of antibiotics, harmful events can be addressed by device removal, which can be easily and safely done at any time, even by patients, by simply grasping the outer tab of the device and pulling it straight out.</p>																																	
<p>Risk from false-positive or false-negative results for diagnostics</p>	<ul style="list-style-type: none"> - What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan? 	<p>N/A</p>																																	

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
<ul style="list-style-type: none"> · Quality of the study design 	<ul style="list-style-type: none"> - How robust were the data? 	<p>Data were robust as the study compared the device to the current standard of care, clinically appropriate endpoints were selected and all results were statistically significant.</p>

· Quality of the conduct of the study	<ul style="list-style-type: none"> - How was the trial designed, conducted and analyzed? - Are there missing data? 	<ul style="list-style-type: none"> -The trial was designed with direction from and the approval of an IDE by the FDA and monitored by Quintiles, a major CRO. -There are no missing data. The subjects who passed the one-week screening and continued to use the device were followed to assess the primary endpoints. Safety data were recorded for subjects who dropped out.
· Robustness of the analysis of the study results	<ul style="list-style-type: none"> - Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results? 	<ul style="list-style-type: none"> -Study results are repeatable. -This study was not the first of its kind. -Study results are consistent with those from six other clinical studies, all of which concerned similar patient populations and all of which reported similar results.
· Generalizability of results	<ul style="list-style-type: none"> - Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups? 	<ul style="list-style-type: none"> -The results of the study are limited to women with atonic bladder and other females with bladder emptying disorders that are the result of neurologic disease or injury.
Characterization of the Disease	<ul style="list-style-type: none"> - How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress? 	<ul style="list-style-type: none"> - Atonic means “no tone” – they cannot generate bladder pressure and so cannot urinate spontaneously. Most require urinary catheters to void, which has both medical and psychological consequences. -Atonic bladder is generally incurable. -Atonic bladder can either be the result of a discrete event, such as stroke, or the result of a progressive disease, such as MS.
Patient tolerance for risk and perspective on benefit	<ul style="list-style-type: none"> - Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable? 	<ul style="list-style-type: none"> -The pivotal study compared the rate and severity of device-related risks to those for the standard of care. -The risks associated with device use are identifiable and definable, as they are similar to those for urinary catheters.
Disease severity	<ul style="list-style-type: none"> - Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit? 	<ul style="list-style-type: none"> -The medical and psychological problems related to atonic bladder are such that most patients are willing to tolerate a higher amount of risk for a smaller benefit.
Disease chronicity	<ul style="list-style-type: none"> - Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies? 	<ul style="list-style-type: none"> -Since atonic bladder is incurable, most patients live with it on a chronic basis. -How long patients live generally depends on the nature of the primary medical condition responsible for their atonic bladder (SCI, stroke, advanced MS, Parkinson’s, diabetic neuropathies, etc.). -Atonic bladder can be managed on a chronic basis with urinary catheters; however, many women are not capable of self-catheterizing and indwelling catheters cause frequent infections and erode self-image.

Factor	Questions to Consider	Notes
Patient-Centric Assessment	<ul style="list-style-type: none"> - How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment? 	<ul style="list-style-type: none"> -Letters from patients and their families state that they consider this treatment transformational. -Patients are willing to take the risk of this treatment to achieve the benefit in increased quality of life. For most, the only risk is that they may find the device too uncomfortable to use, in which case they can simply remove it. -Clinical studies show that the treatment improves quality of life by 60-80%. -As voiding is an activity of daily living and most of us void 4-8 times per day, most patients clearly understand the benefits and risks of the treatment.
Availability of alternative treatments or diagnostics	<ul style="list-style-type: none"> - What other therapies are available for this condition? - How effective are the alternative treatments? - How does their effectiveness vary by subpopulation? - How well-tolerated are the alternative therapies? - How does their tolerance vary by subpopulation? - What risks are presented by any available alternative treatments? 	<ul style="list-style-type: none"> - While new procedures (notably the Medtronic InterStim and Allergan Botox) now provide alternatives for neurogenic <i>overactive</i> bladder, none have emerged for neurogenic <i>underactive</i> bladder, i.e. atonic bladder. The vast majority of women with atonic bladder use urinary catheters for bladder drainage. -The only currently available “treatments” for atonic bladder are urinary catheters, which significantly decrease quality of life and in the case of Foley catheters, also cause frequent infections, skin problems, etc. -Their effectiveness does not vary by subpopulation. -The problems related to urinary catheters are heightened for women with atonic bladder, as it is an incurable condition and they have to live with the problems on a life-long basis. -Tolerance is better for post-operative patients and others who need urinary catheters for short periods. -The risk presented by the two available alternative treatments are as follows: 1) CIC degrades quality of life as it requires that a patient insert a tube into their bladder 120-240x per month and 2) Foley catheters require that patients have a tube coming from them, be tied to a bag of their own urine and suffer frequent infections.
Risk mitigation	<ul style="list-style-type: none"> - Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed? 	<ul style="list-style-type: none"> -Most risk mitigation was performed pre-market in the form of: a) laboratory testing to ensure that device components do not cause cytotoxic response, irritation, or sensitization, b) substantial clinical testing to ensure safety with chronic use and in the event of device failure or user error and c) revised product labeling intended to increase the rate of device acceptance. Post-clearance, the company plans to standardize training for device best practice, first by establishing a limited number of centers of excellence and then by online CME-type courses and patient videos. -Similar pre-market testing is proposed for any new intraurethral device.

