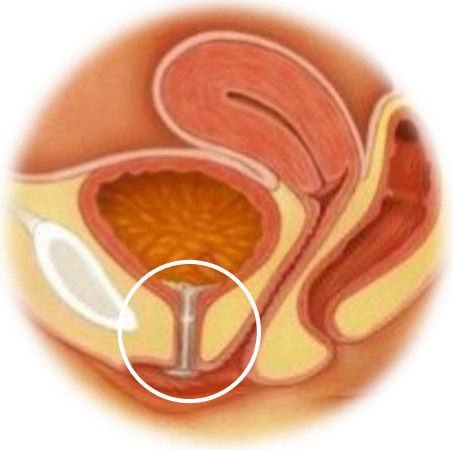
The inFlow™ Urinary Prosthesis for Women with IDC



The inFlow Intraurethral Valve-Pump ("the inFlow device" or "the inFlow") is a non-surgical urinary prosthesis that provides bladder drainage for women with incomplete bladder emptying due to impaired detrusor contractility (IDC). The inFlow mimics normal urination, providing a convenient and dignified alternative to urinary catheters. (It is not an incontinence device.) The inFlow is normally replaced every 29 days, but can be easily and safely removed at any time, even by patients.

IDC Background

Impaired detrusor contractility (IDC) is the inability to contract the muscles necessary to push urine out of the bladder. IDC is most often the result of life-altering neurologic disease or injury such as multiple sclerosis, spinal cord injury, spina bifida, stroke, or diabetic neuropathies. IDC (a/k/a atonic bladder) is itself a serious medical problem and complications include urinary retention, overflow incontinence, recurrent UTIs, bladder stones and impaired renal function.

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

Medical technology has made amazing advances in many areas, but urinary catheters are not among them.

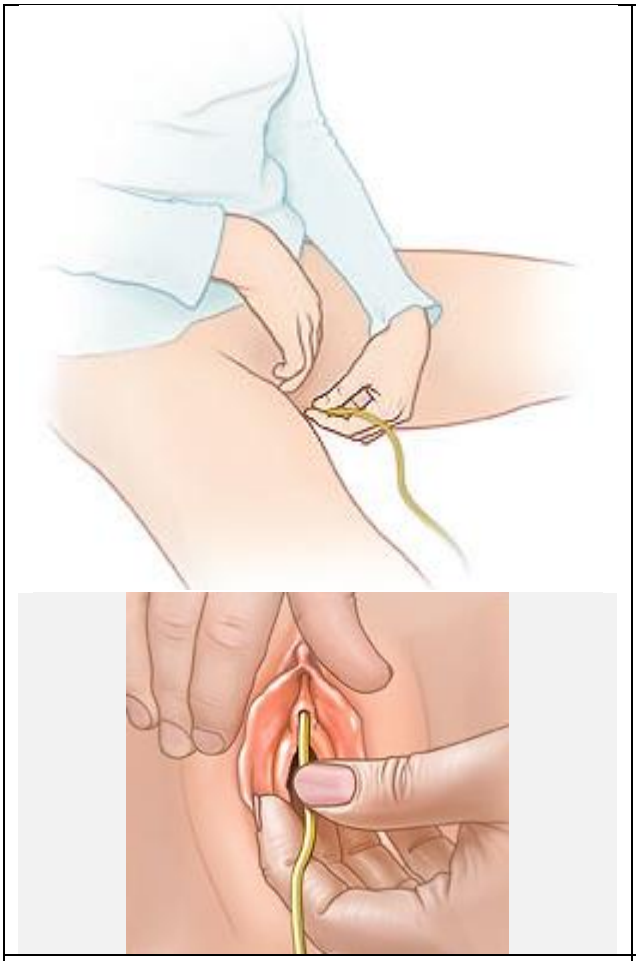
"The basic design of the catheter in use today has not changed since it was first invented in 1937"

Urinary catheters may be the most commonly used of all medical devices; however, with chronic use they often cause serious problems, notably:

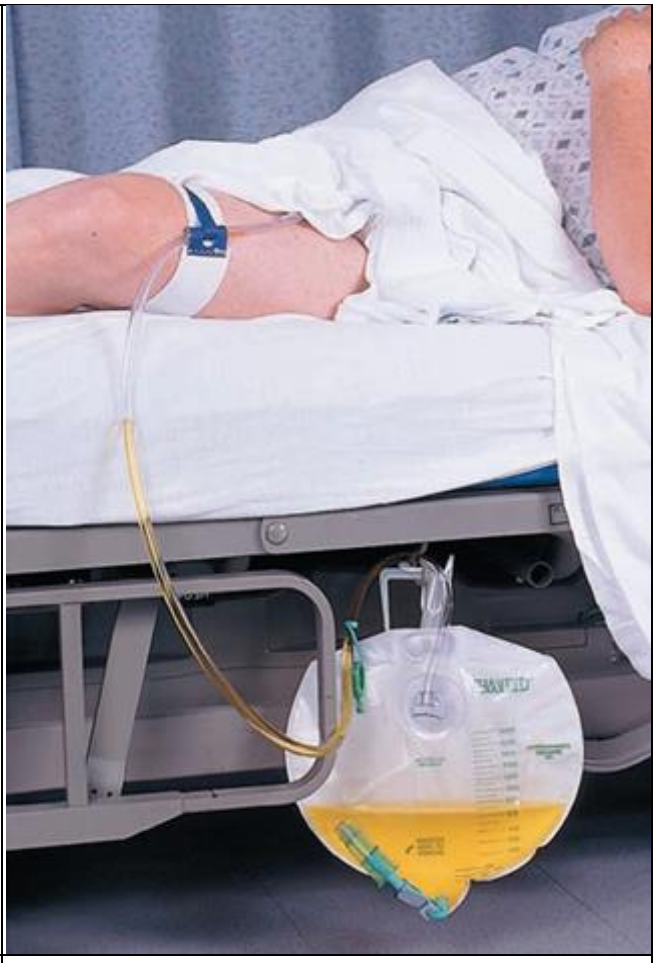
1. urinary tract infections (UTIs),
2. low quality of life (QOL), and
3. encrustation (right).

These problems are acutely heightened for women with IDC, since they must use urinary catheters every day for their entire lives.

Women with IDC are currently an underserved population and in acute need of improved methods of bladder drainage. Currently, most have only two choices:



They can insert a tube into their bladder 4-6 times a day (240 times per month)



They can tie themselves to a bag of their own urine and resign themselves to frequent infections

The present standard of care for women with IDC is clean intermittent catheterization (above left), which is thought to have a far lower UTI rate than indwelling (Foley) catheters (above right). Since CIC requires a tube to be inserted into the bladder 4-6 times per day; however, 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 low quality of life and high rate of UTIs that invariably result.

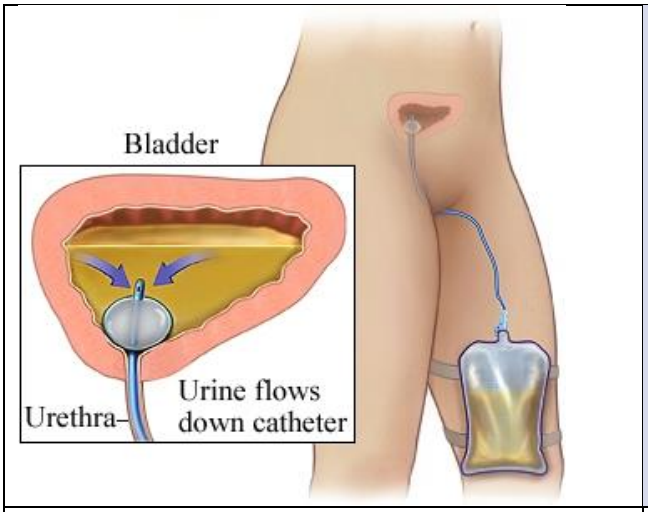
- Per the CDC, UTIs from Foley catheters cause over 13,000 deaths and add $1.85 Billion in direct medical costs annually in U.S. hospitals alone. These figures are for 2002, the most recent year with published data, and may be higher now. The CDC has stated that *"Antimicrobial resistance among urinary pathogens is an ever increasing problem".*

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.

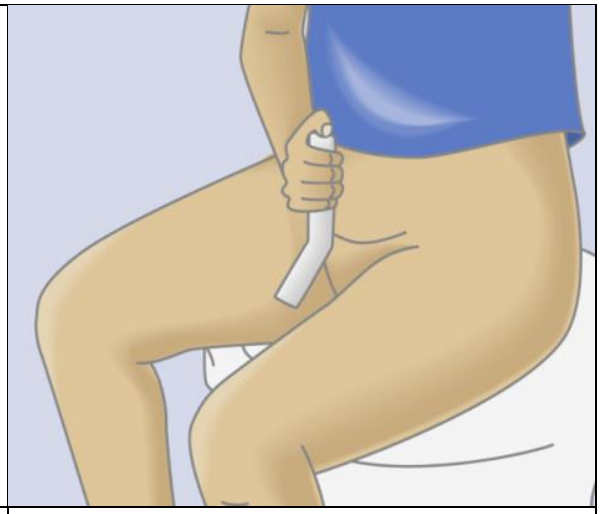
As crucial as it is, women with IDC currently have virtually no hope of regaining the ability to void normally.

Advanced Technology for More Natural Bladder Drainage

The inFlow device is intended to normalize their toileting to the greatest degree possible. As a prosthetic device, it is designed to compensate for a specific anatomic deficiency. The inFlow's internal pump compensates for the inability of women with IDC to generate bladder pressure by providing forceful, virtually complete evacuation of urine on demand. By allowing almost normal use of a toilet, the inFlow eliminates the need to catheterize multiple times daily and eliminates tubes/drainage bags, improving its users' self-image as well as their hygiene.



Bladder drainage with indwelling catheter and drainage bag



Bladder drainage with the inFlow and normal toilet

In short, the inFlow is intended to restore personal dignity to a group of women who are sorely in need.

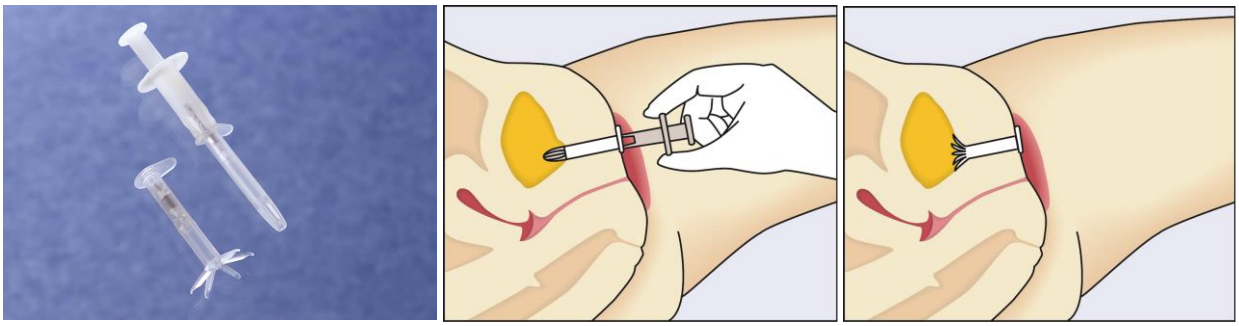
Table A. Bladder Drainage Comparison

	inFlow	CIC	Foley
Minimal UTI rate	🟢	🟢	🔴
Effectively empties bladder	🟢	🟢	🔴
Allows bladder cycling	🟢	🟢	🔴
Easy to operate	🟢	🔴	🟢
Allows use of toilet	🟢	🔴	🔴
Insertions required/per month	1	120-200	1

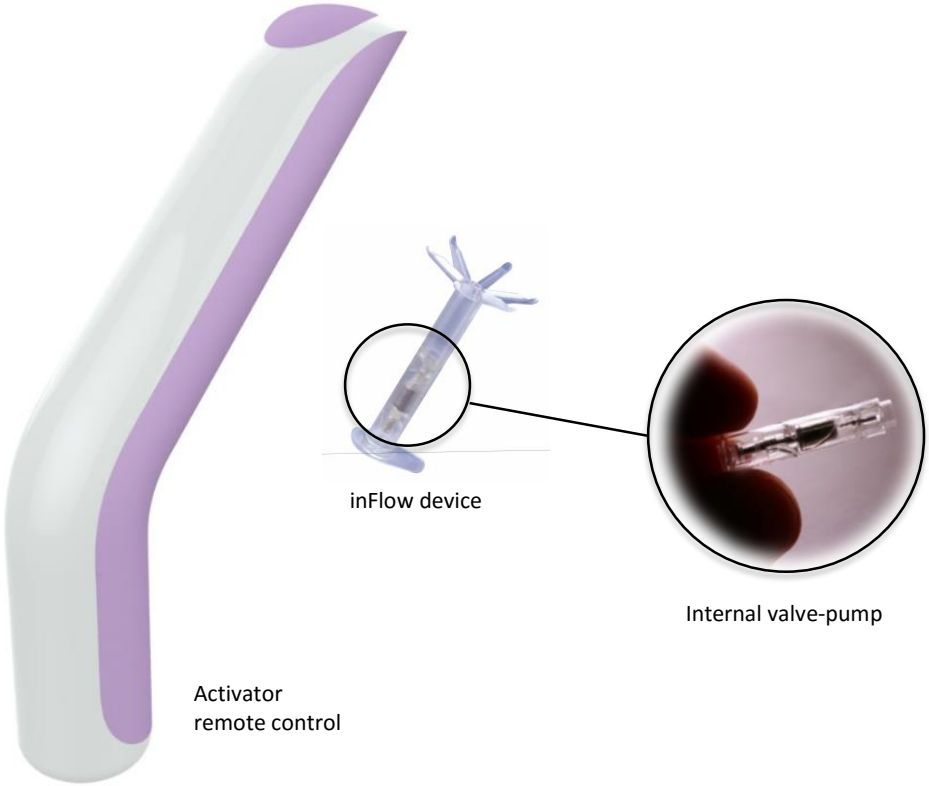
inFlow Indication for Use

Per its FDA approval letter of October 14, 2014, the inFlow Intraurethral Valve-Pump ("inFlow device") with Activator was down-classified from Class III to Class II via the *de novo* pathway and is indicated for use "in female patients 18 years of age or older who have incomplete bladder emptying due to impaired detrusor contractility 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)."

How the inFlow Works



The inFlow is a 3-7cm long device in a silicone housing (left, with its disposable introducer and underneath following device deployment). Device sizing and initial insertion is performed by a physician. Thereafter, a new device is inserted every 29 days, typically by a caregiver or spouse. Insertion is similar to that for a urinary catheter (middle). The inserted device resides almost entirely in the urethra (right) so that only the user knows it's there. To void, the user sits on a toilet, holds a remote control over the lower pelvic area and presses a button. This magnetically activates a miniature internal pump that drains the bladder at a normal flow rate. When the button is released, a valve is engaged, blocking further urine flow.



Extensive data from a variety of sources exists regarding the inFlow's safety and effectiveness.

Non-Clinical Laboratory Testing

As summarized in **Table B**, comprehensive laboratory testing of the inFlow has been conducted:

Table B. List of Laboratory Testing

Test Type	Tests Made
Risk Management	As confirmed by a 2013 audit by its notified body, the inFlow device conforms to ISO 14971, an FDA-recognized standard, and so has been designed to deliver the most benefit for the least amount of risk.
Biocompatibility	The FDA classified the inFlow device as a permanent surface device with mucosal membrane contact and per ISO 10993-1:2009 (Biological Evaluation of Medical Devices), the following biocompatibility tests were performed on final, sterilized samples: 1. ISO 10993-5 Cytoxicity 2. ISO 10993-10 Sensitization 3. ISO 10993-10 Irritation 4. ISO 10993-3 Genotoxicity 5. ISO 10993-6 Implantation (for both 13 weeks and 26 weeks) Furthermore, the following additional tests were performed re the systemic toxicity of device materials: • 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 Per the FDA "The results of this testing support the biocompatibility of the inFlow device for its intended use."
Sterilization	ISO 11137-2, Sterilization of Health Care Products - Radiation
Additional Applicable Standards	• 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 3 kHz to 300 GHz)
Device-Specific Tests	Device performance meets or exceeds the following: • High Pressure Test (seal maintained under 200 cm H20 bladder pressure) • Catheter Pump and Valve Endurance Test (1140 voiding cycles=6 months use) • Activator Endurance Testing (11,552 operation cycles=5 years) • Activator Drop Testing (50 cm onto hard surface) • Activator Battery Endurance Testing (2 months)
Encrustation Resistance	An *in vitro* study by Stickler 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).

Pivotal Trial

An 18-site, single-arm crossover study (*n*=273) was performed to compare safety, effectiveness, and patient satisfaction of the inFlow device versus clean intermittent catheterization ("CIC"), the current standard of care for long-term bladder drainage. The study was limited to females with atonic bladder who were successfully using CIC. 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.

As shown in **Table C**, the results of the pivotal study were positive and unambiguous.

Table C. Summary of Pivotal Trial Results

	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 ±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**

1. Primary Endpoint: Post-void residual (PVR). All subjects with PVR data available for both Baseline and Treatment were considered to be evaluable. This resulted in a total of 115 evaluable subjects (including some dropouts). 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.

2. Secondary endpoint: Quality of life (QOL). Among those subjects with both Baseline and Treatment QOL data, 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.

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 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 the finding of equivalence is notable in that no *indwelling* bladder drainage device has ever been shown to have the same UTI rate as *intermittent* catheters.

   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. Device awareness/ discomfort increased during inFlow Treatment and although all cases were mild in severity, this caused numerous subjects to discontinue device use. The discontinuance rate was similar to that reported for contact lenses, which also elicit foreign body awareness. Per post-analysis, the safety profiles for subjects who withdrew from the study (non-completers) did not differ significantly from those who completed the study.

The FDA's report of the inFlow's pivotal trial was published in October 2014 and is available online:

http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130044.pdf

This study has also been described by two Clinical Investigators, Drs. Tu and Kennelly:

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.

Investigator-Sponsored Clinical Studies

In addition, six investigator-sponsored clinical studies (total *n*=228; utilizing the marketed device outside the U.S.) have been published in major peer-reviewed journals:

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.

All six clinical studies concerned similar populations to the pivotal study and for the most part reported similar findings. Study 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.

Table D. Summary of Investigator-Sponsored Clinical Studies

PI/Lead Author	Study Size	Conclusions/Key Findings
Mazouni (2004)	60	*"An attractive, simple technique for use as an alternative to catheterization."*
Lynch (2003)	20	Reported 80% improvement in quality of life (QoL) and no negative tissue changes. "*This study shows that the (inFlow) device provides an effective method of bladder drainage, with few side-effects and significant improvement in QoL."*
Madjar (2000)	21	Reported that although dropout was a problem (due largely to discomfort), *"Women who continue treatment for a prolonged time are satisfied with the device use." In fact, "All patients were satisfied with the device and preferred it to previous treatment modalities used."*
Madjar (1999)	92	Reported only 3.9% of subject months with UTI in 357 months of device use and all resolved with oral antibiotics.
Schurch (1999)	18	Early study suffered from poor product quality.
Nativ (1997)	17	2 of 14 subjects subsequently recovered bladder function (as did 8 subjects in other studies, total 10/228=4.4%).
Totals	228	207 unique subjects (Madjar's studies were continuous for same cohort)

No serious or lasting adverse events were reported in any study and the Lynch study reported a high rate of device acceptance. That study and the more recent study by Madjar et al. followed a total of 41 women for at least a year. These three long-term studies are summarized in the following sections.

Lynch et al

In a one-year study of 20 acontractile (atonic) 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 enrollment, 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 affect 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

In a study of 21 patients with voiding dysfunction who were followed for more than a year with a follow-up time of 12-44 months (mean 24.6 months), Madjar et al. demonstrated similar results to the pivotal study with respect to bladder emptying (post-void residual), complications, and reasons for withdrawal.

This study was a continuation of a previous study of 92 women, age 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. The cause 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 U.S. pivotal study, in which 99% of patients were CIC users, this study included patients whose previous treatments included indwelling catheter (*n*=21) and no treatment (*n*=16), as well as CIC (*n*=55).

All patients received the inFlow device at the start of the study. Patients 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, as of the most recent follow-up. Of the latter, 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. 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, 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.

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 study 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 and cost. Device deficiencies have long since been corrected. With regard to cost, the investigators note that:

> "The prosthesis is marketed at €160, the first implanted prosthesis was provided by the department, but the others were at the patient's cost."

The investigators also make two interesting observations with regard to the abandonment/ discontinuance rate:

> "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 atonic bladder 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."

Clinical Use Outside the U.S.

The inFlow has been sold outside the U.S. for over ten years, mostly in Europe, Australia, Israel and Canada. Some 15,000 devices have been sold to date, amounting to over *1,200 women-years of use* based on typical device use of one month each. Per ISO-audited complaint files, no serious adverse events have ever been reported. Vesiflo has just re-launched the inFlow in Germany, where it is reimbursed by that country's national health system (**GMDN Code** 32597 Prosthesis, internal, tube, urethra).

Recent Clinical Experience in the U.S.

Although its pivotal study clearly established the safety and effectiveness of the inFlow urinary prosthesis, it also indicated that many women have difficulty tolerating the inFlow device. Specifically, approximately half of the subjects elected to discontinue using the inFlow device within the first two weeks of device use due to discomfort or urine leakage around the device.

Following the pivotal study; however, 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 the 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 standard rehab protocol, they started by setting appropriate patient expectations prior to initial device insertion, i.e. disclosing the risk of discomfort, but also explaining that any discomfort was 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 study, where "implantation" of the device was treated as similar to a surgical procedure and discomfort was considered an adverse event warranting dismissal of subjects from the study.

The effectiveness of the Lynch protocol has been confirmed by recent clinical experience, which has shown a device acceptance rate of approximately 80% with all comers. To date, most device discontinuance has been the result of patient preference and only one patient discontinued device use as the result of discomfort. Although a number of patients have experienced leakage, this is no longer a major cause of device discontinuance as it either resolves as patients accommodate to the device or is managed with medication. (Subjects in the pivotal study were not allowed to take additional medications.)

In the two months since the advance release of the inFlow Activator 2.0, Vesiflo has in-serviced clinicians in 8 U.S. cities and enrolled 25 patients suffering from a variety of neurogenic bladder complexities:

- 7 Multiple Sclerosis patients
- 4 Diabetic Cystopathy patients. One of these patients, who had a history of 2-3 hospital admissions per year for UTI treatments, is so pleased with the inFlow that she wants to be a spokesperson.
- 2 Spina Bifida Patients
- 1 Multiple System Atrophy Patient. This patient had post void residual levels of 800 CC or more; however, due to her inability to abduct her legs, her dedicated team of health care providers were no longer able to use intermittent catheterization for her bladder drainage. As a last step prior to transitioning her to an indwelling catheter, an inFlow device was placed. This was very successful and she is now able to enjoy nights out with friends, movie dates with her spouse, and is regaining the ability to manage her own bladder health and emptying.
- 2 Organ Failure Patients
- 1 Hydronephrosis Patient. A repeat kidney ultrasound on this patient showed that she was able to resolve her hydronephrosis with frequent, forceful and complete bladder emptying by using the inFlow device on a voiding schedule specifically designed to meet her needs.
- 1 Lupus Patient
- 3 Patients with unknown reasons for Urinary Retention
- 4 Age vs. Idiopathic Retention

With additional clinical experience, it is increasingly clear that bladder dysfunction cannot be managed in isolation; most inFlow candidates also struggle daily with serious primary medical conditions that affect both other bodily systems and their behavior. Vesiflo has come to understand that is it necessary not only to retrain the bladder to fill and empty on a timed cycle, but also to rehabilitate patients to a pattern of good bladder health that includes timed voiding, staying hydrated every day and other healthy behaviors.

This requires a comprehensive approach that addresses the individual needs of patients and works in conjunction with their loved ones and health care providers, so Vesiflo's clinical team stays in frequent contact with every patient and every physician for the first 60 days following initial insertion. This also reaffirms the need for the Guardian™ Voiding Care System (VCS), Vesiflo's development-stage mobile health system based on the new "smart" Activator 2.0, which will provide patient support, remote monitoring and Big Data concerning the effectiveness of interventions for patients with neurogenic bladder.

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.

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