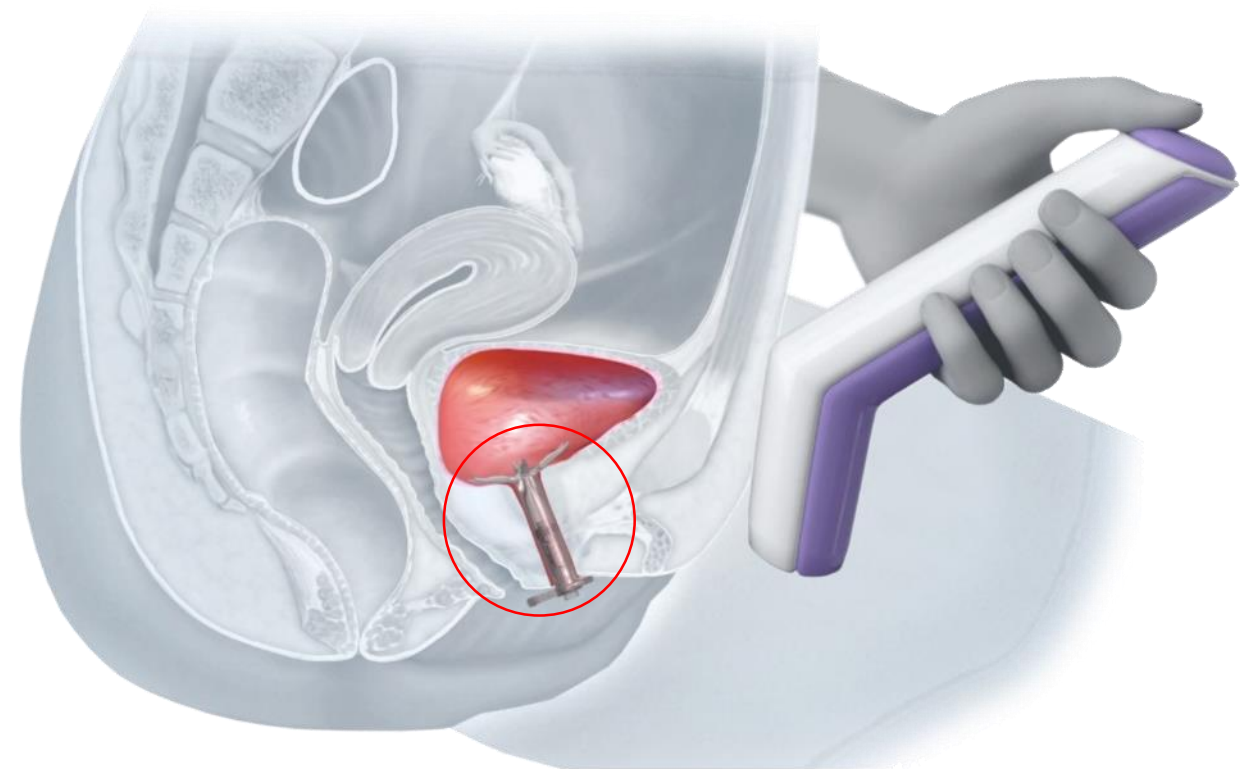


Background and Clinical Evidence: **inFlow[™] Urinary Prosthesis** FDA De Novo Approval DEN130044

- Unique alternative to urinary catheters for women with permanent urinary retention
- Therapeutic benefits
 - Highly effective in emptying the bladder
 - Lower UTI rate than current standard of care, CIC (clean intermittent catheterization)
 - Significantly improves quality of life
- Same or lower cost as CIC



Overview

- Women with permanent urinary retention (PUR) have almost no medical alternatives
 - Virtually all use urinary catheters every day of their lives, but not all are well served by this
 - PUR is often the result of life-altering neurologic disease or injury and these women are a generally fragile patient population
- The inFlow™ Urinary Prosthesis is an innovative alternative to urinary catheters that can restore function and dignity to women with PUR
 - Mimics normal urination vs. bladder drainage with a tube
 - 29-day device whose pivotal trial showed it to have a lower UTI rate than the current standard of care, intermittent catheters (CIC), and also to improve quality of life by 60%



Presentation



1. Burden of Illness
2. Product Information
3. Value Evidence Supporting Technology
4. Future Directions and Applications

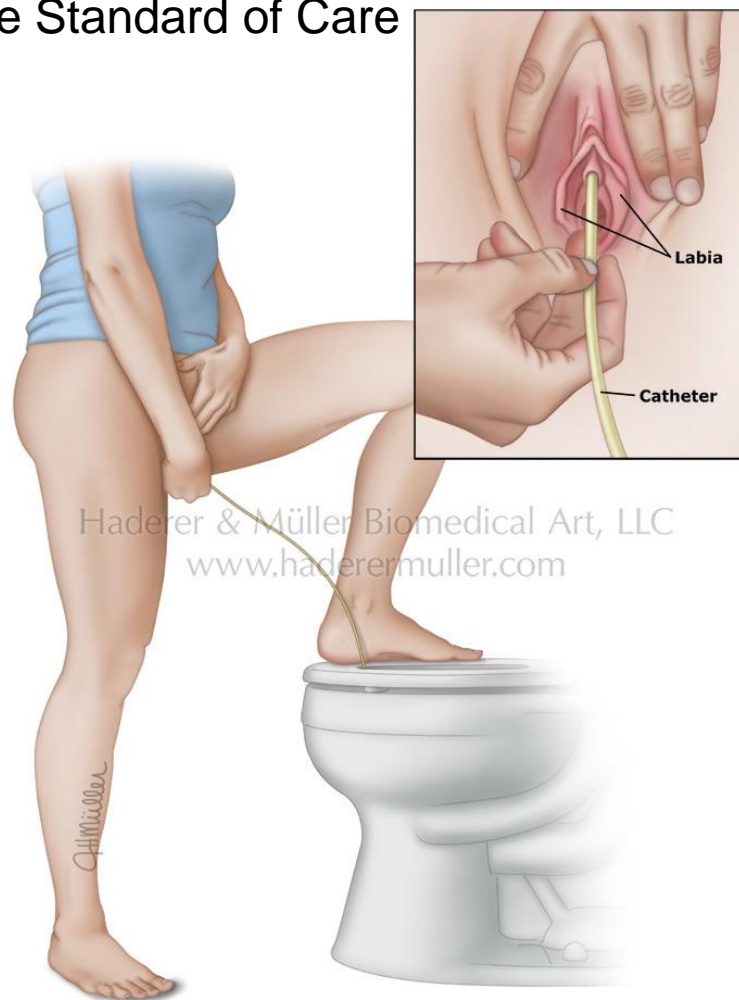
Note: This presentation follows the same format as the inFlow Evidence Dossier

Present Medical Alternatives

- Most women with permanent urinary retention use one of two types of urinary catheters

Intermittent catheters (CIC)

The Standard of Care



A tube is inserted into the bladder 4-6+ times per day (200x per month)

Indwelling catheters (usually a Foley)

The Only Alternative to CIC



A tube connected to a urine bag remains in the bladder at all times



Medical technology has made amazing advances in many areas

Bladder drainage is not among them

- Catheters are believed to have been invented in ancient Egypt, 3500 years ago
 - River reeds were often used
- Arguably, the only significant technology advance since then is the use of new materials



The Problem

Catheter-associated urinary tract infections (CAUTI) kill people

- *Attributable deaths estimated to be over 13,000¹*

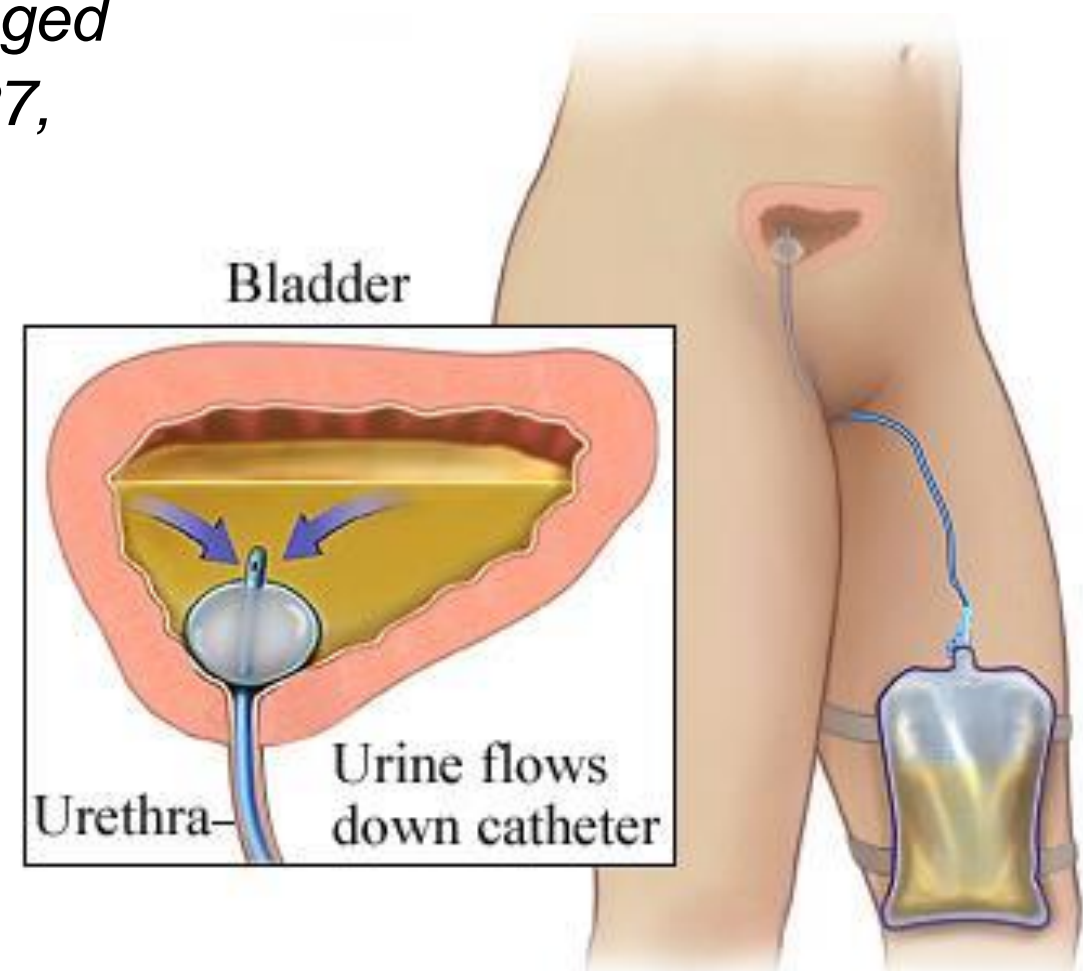
And things are not likely to improve any time soon

- *Per the CDC, “Antimicrobial resistance among urinary pathogens is an ever increasing problem”²*

1. 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
2. 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>

The Perfect UTI Generator?

"..fundamental problems with the basic design of the catheter, which has changed little since it was first introduced in 1937, induce susceptibility to infection"^{3,4}



The most commonly used urinary catheter
requires users to be literally tied to a bag of their own urine

3. Feneley RCL, Kunin CM, and Stickler DJ. *An indwelling urinary catheter for the 21st century.* BJU International, vol. 109, no. 12, pp. 1746–1749, 2012
4. Foley FE. *A self-retaining bag catheter for use as an indwelling catheter for constant drainage of the bladder.* J Urol, 1937

Image © Healthwise, Incorporated

Urinary Catheters Cause a Variety of Problems

■ Encrustation

- As many as 50% of indwelling catheter users experience blockage due to encrustation⁵
 - Highly distressing to patients- can result in leakage around the catheter, urinary retention, pain and urethral trauma on catheter removal



■ Low quality of life

- Chronic catheterization can be psychologically devastating
 - The ability to void is a basic daily function and loss of this ability erodes our self-image as independent adults
- Chronic catheterization makes demands on the most vulnerable
 1. Patients must either self-catheterize, a procedure so burdensome that the long-term compliance is low, ⁶ OR
 2. Use a Foley catheter and urine bag, which many regard as an end-stage development and certainly the end of their social lives



■ High level of complications (not a complete list)

- Hematuria, pain, leakage, bladder spasm, loss of bladder function (particularly in the elderly), bladder calculi, bladder neck erosion (patulous urethra) and genitourinary injury that includes traumatic injury to urethra, bladder and surrounding structure during catheter insertion or removal⁷

5. Getliffe K. *Managing recurrent urinary catheter encrustation*. Br J Community Nurs 2002; 7:574,576, 578-580

6. Girotti ME, MacCornick S, Perissé H, Batezini NS, Almeida FG. Determining the variables associated to clean intermittent self-catheterization adherence rate: one-year follow-up study. Int Braz J Urol. 2011 Nov-Dec; 37(6):766-72.

7. Robinson J (2004) A practical approach to catheter-associated problems. Nursing Standard. 18, 31, 38-42. Date of acceptance: December 16 2003


The Population Most Affected

- Diagnostic terminology for permanent urinary retention varies, but an increasingly common term is impaired detrusor contractility (IDC)
 - Caused by neurologic disease or injury (diabetes, advanced MS, spinal cord injury, multiple system atrophy, pelvic surgery, etc.)
- Due to its neurologic basis, IDC is generally incurable and typically requires life-long use of urinary catheters
 - Women with IDC lead challenging lives as a result of their primary medical conditions, leaving most with limited physiological or psychological resources to deal with this or other issues related to their IDC



Estimated U.S. IDC Prevalence

Vesiflo estimates there are approximately 470,000 U.S. women with IDC as a result of their neurologic condition:*

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

Based on clinical experience to date, about 1/2 are device candidates (235,000 women)

These neurologic conditions are life-altering and most women with IDC are Medicare eligible as a result of disability and/or age

* Please refer to Exhibit A: Estimated Number of U.S. Women with IDC

Exhibit A: Est. Number of U.S. Women with IDC

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 impaired detrusor contractility and then applies the IDC prevalence for each condition. The definition used in this analysis is IDC requiring use of urinary catheters.

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 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.

Parkinson’s – 41,250 U.S. Women

“About 1 million Americans are thought to have Parkinson’s,” of which ~ 330,000 are women.⁸ “20% to 30% of women with Parkinson-related syndromes will have urodynamic findings of detrusor hypocontractility or areflexia.”⁹ (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.

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.¹⁰ 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.

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 ¼ 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.

1. MS Society. (2017) *Preliminary Results of MS Prevalence Study Estimate Nearly 1 Million Living with MS in the U.S.* News Release. <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.

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

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

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

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

Presentation



1. Burden of Illness
2. Product Information
3. Value Evidence Supporting Technology
4. Future Directions and Applications

Indication for Use

The inFlow Intraurethral Valve-Pump and Activator

is a replaceable urinary prosthesis
intended for use in adult females
who have incomplete bladder emptying
due to impaired detrusor contractility
of neurologic origin

Must be replaced every 29 days

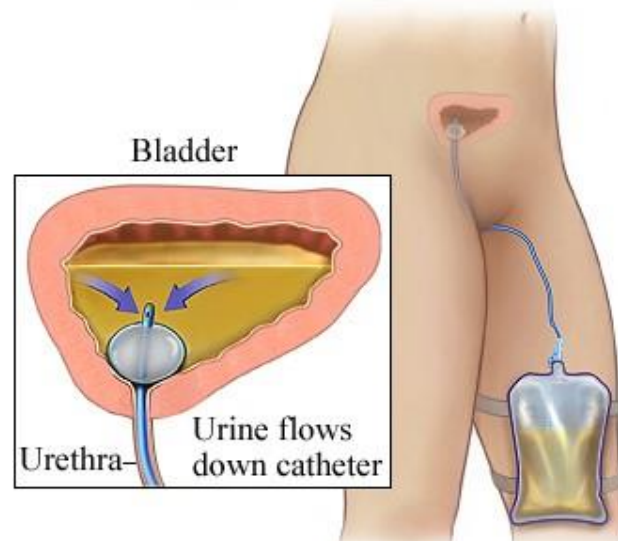


Deployed device shown on left and as packaged
with disposable introducer on right

What is a Urinary Prosthesis?

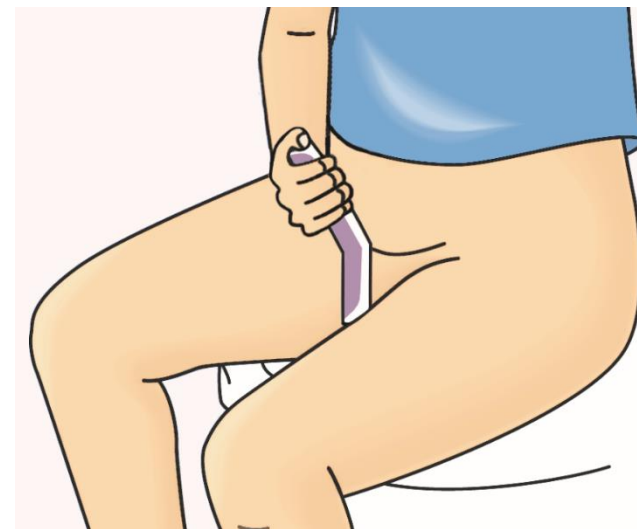
- A prosthesis is a device that replaces a missing body part or function
 - Women with IDC lack the bladder function to urinate –inFlow replaces their bladder function by pumping their urine out at a normal flowrate
 - This allows them to use a toilet in a more typical and dignified way
- Catheterizing vs. using inFlow is comparable to the difference between IV feeding and eating – both supply nutrition, but they do it quite differently
 - Likewise, both catheters and inFlow drain the bladder, but their methods and effects differ

*Catheters are tubes that **passively** drain urine*



Bladder Drainage

*inFlow is an **active** device that mimics normal urination*

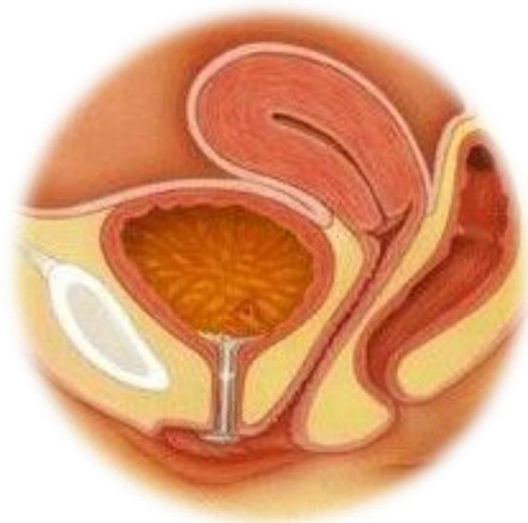


Normalized Urination

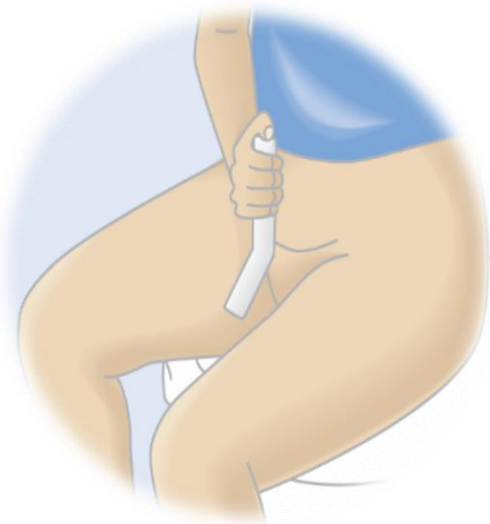
- Normalizing urination can have profound psychological as well as medical benefits

How the inFlow Works

*Employing Unique Magnetic Coupling Technology**



inFlow device is inserted into urethra and remains in place for 29 days

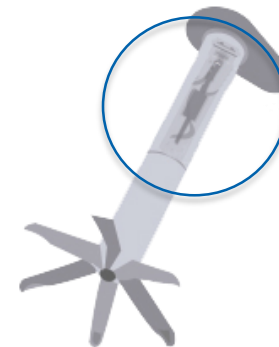


To void, the patient sits on a toilet and pushes a button on the Activator



Activator remote control

inFlow device



This activates an internal pump that PUMPS the urine out at a normal flow rate

* As described in U.S. Patent Numbers 9,839,373 and 5,762,599

New Approach to an Age-Old Problem

How do you get urine out of the bladder without causing infection?

- Most recent efforts have concerned use of antimicrobial coatings intended to retard the growth of biofilm on catheter surface
 - It's fair to say that to date this approach has not resulted in clinically significant improvement⁸

How does the body normally protect itself and how does a catheter interfere?

- Good bladder health requires three voiding-related functions
 1. Periodic
 2. Forceful and
 3. Complete bladder emptying
- An indwelling urinary catheter provides none of these functions, but by normalizing urination the inFlow maintains all of these key functions

$$3\text{Hrs} \times 14\text{cc/sec} = \text{PVR} < 50\text{cc}^*$$

The inFlow Formula for Chronic Urinary Retention

Explained:

Periodic (every 3 hours),
Forceful (intraurethral pump @ 14cc/sec)
Complete Bladder Emptying (PVR <50cc)

= **Simulated Micturition**

*10cc typical

8. Pickard R, Lam T, MacLennan G, et al. *Antimicrobial catheters for reduction of symptomatic urinary tract infection in adults requiring short-term catheterisation in hospital: a multicentre randomized controlled trial*. Lancet. 380:1927–1935 (2012)

The inFlow's Clinical Role

- Women with IDC have very few alternatives currently

	Intermittent Catheter (CIC)	Indwelling Catheter	inFlow
Low Infection rate	●	●	●
Easy to use	●	●	●
Hygienic	●	●	●
Positive body image	●	●	●
Normalizes urination	●	●	●
No. Insertions per Mo.	150-200	1	1

- The standard of care is CIC, but not all women with IDC can use this method
 - Due to their disabling primary medical conditions, many lack the dexterity or visual acuity to safely perform self-catheterization, making CIC impractical
 - Their only alternative presently is use of an indwelling catheter (usually a Foley catheter) despite the high UTI rate and low quality of life known to result
- In clinical practice, the inFlow is used when patients have failed CIC or if a physician thinks the patient will be better served by this device

Physician-Controlled Device

- **Visit One:** Patient with established IDC presents herself for evaluation by urologist
 - Urethral length is measured with inFlow Sizing Device to determine correct device size (9 sizes, range 3-7cm length)
 - Cystourethroscopy may be performed to confirm tissue integrity
 - Anticholinergics may be prescribed
- **Visit Two:** Physician inserts initial device, trains patient in Activator use and device removal/replacement
 - Spouse or caregiver is highly recommended for training as well
 - Physician instills saline into patient's bladder and confirms her ability to void with device in place
 - Physician schedules follow-up visits every 6 months or as needed per patient condition and establishes point-of-contact for routine RN support
- Monthly device replacements can be performed by spouse, caregiver or clinician
 - In Europe, most device replacements were done by spouse or caregiver
 - In limited U.S. use, most replacements are being done by a clinician



Presentation



1. Burden of Illness
2. Product Information
3. Value Evidence Supporting Technology
4. Future Directions and Applications

FDA History as a Class III Device

- The FDA classified inFlow as a Class III device and required that a pivotal trial be conducted under IDE G970029 in support of a PMA (premarket approval) application
- Vesiflo submitted data from a prospective, multi-center* pivotal trial ($n=158$) that compared inFlow to current standard of care, clean intermittent catheterization (CIC)
 - Additional evidence included:
 - Six non-comparative clinical studies (total $n=228$), three of which were long-term studies of 1-4 years and all of which were published in major peer-reviewed journals
 - Real-world experience as documented by ISO-audited complaint files for 1,250 women-years of clinical use OUS with no MDRs or significant safety issues
 - Animal and laboratory test reports showing conformance to the most recent ISO 10993 biocompatibility standards for a permanent surface device with mucosal membrane contact
 - Laboratory test reports showing conformance to ISO, ASTM and other established industry standards for urinary catheters
 - A microbiology study showing >8.4x better encrustation resistance than current standard of care
- Following analysis of all evidence by FDA's most senior scientific and medical reviewers, the inFlow was approved and in the process down-classified from Class III to Class II
 - Its approval via the De Novo pathway established the inFlow as a new type of device (CFR §876.5140)

* 15 US sites, 3 sites OUS

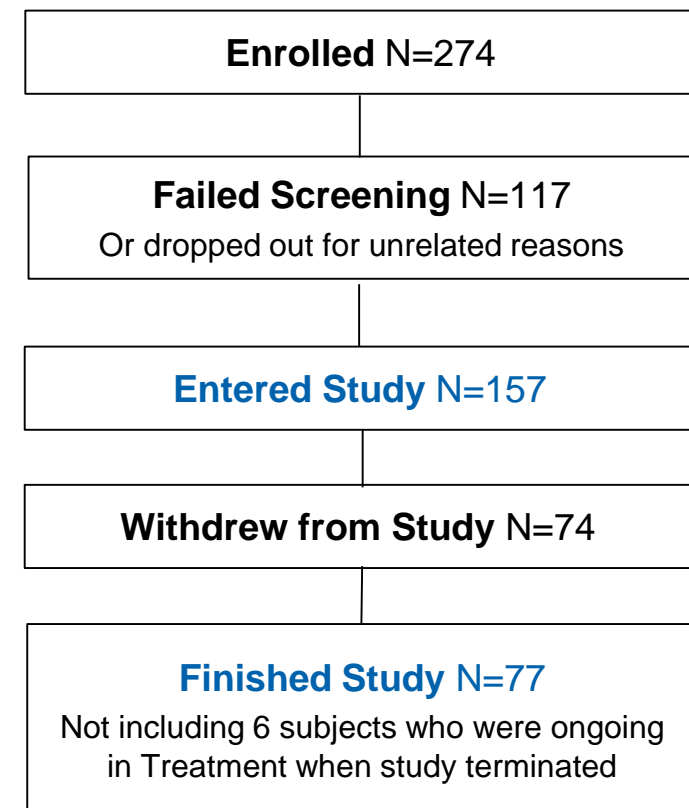
Pivotal Trial Design

- Study compared the inFlow to the current standard of care (CIC) and did so with a cohort for which CIC was their normal method of bladder drainage
 - Study limited to women who were successfully using CIC, some for as long as 20 years
 - Single-arm crossover design reduced the influence of confounding covariates since each subject acted as her own control
 - CIC use tracked for 8 weeks as Baseline, then switched to inFlow Treatment for 16 weeks
 - As a high dropout rate was anticipated, endpoint data were collected for both dropouts and completers in order to allow retrospective comparisons between groups
- Relevant clinical endpoints were selected
 1. **Primary Endpoint: Post-void residuals (PVRs)** - Indicates how effectively each device performs its primary function, draining the bladder
 - PVRs were considered comparable for a subject if their median inFlow/Treatment PVR was no greater than their median CIC/Baseline PVR, or if both were <50 cc
 - Goal was to have at least 95% of subjects with comparable rate PVRs
 2. **Secondary Endpoint: Quality of life per Wagner I-QOL** – As measured on a 100-point scale using a validated instrument commonly used for voiding-related studies
 - Goal was to show equivalence
 3. **Comparative Safety:** Adverse events, particularly the two most serious catheter-related complications, urinary tract infection (UTI) and encrustation

Enrollment Criteria and Subject Flowchart

- Key inclusion criteria
 - Women 18 years of age or older
 - History of successful CIC use
 - Urodynamically confirmed Dx of atonic bladder (now IDC)
 - Capable of determining when to void (either by urge or by adherence to timed voiding schedule) or has caregiver who will attend to bladder emptying at least 4x daily
- Key exclusion criteria
 - Diagnosis and/or treatment of a symptomatic UTI during the two weeks prior to the screening visit
 - Uninhibited bladder contraction >15cm H₂O unless confirmed via UDS as controlled with anticholinergics
 - Neoplastic or inflammatory processes involving the lower urinary tract, uterus, cervix, or vagina
- 115 subjects were considered evaluable for the primary endpoint, including some who did not finish the study

Baseline/CIC = 8 weeks
Then Crossed Over to
Treatment/inFlow = 16 weeks



Primary Endpoint: Post-Void Residual (PVR)

The inFlow and CIC were equivalent in their ability to fully empty the bladder

- 98% (113/115) of evaluable subjects had comparable PVRs, 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%
 - These results successfully met the protocol stated goal of demonstrating a 95% comparable rate with a 95% confidence interval half-width of approximately $\pm 4\%$
 - 92-98% of all subjects had comparable PVRs at every treatment visit
- Subjects were considered evaluable if they had both Baseline and Treatment PVR data
 - There was no statistically significant difference in Baseline PVR between those included vs. excluded in PVR analysis ($P=0.54$ by stratified logrank test)
- The within patient inFlow vs. CIC difference indicated a statistically significant lower PVR on inFlow ($p=0.02$)
 - Both inFlow and CIC were highly effective, with median values well below the 50-100cc level considered acceptable voiding function

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

Secondary Endpoint: Quality of Life (QOL)

The inFlow was significantly superior to CIC in its effect on quality of life

- Incontinence-related QOL was measured by the Wagner I-QOL on a 100-point scale
 - In order to better isolate device-specific affects, responses were analyzed in two parts

Wagner I-QOL Part A - Satisfaction with Current Type of Catheter	N	Mean	Std. Dev	Median	Minimum	Maximum	P-value*
Baseline Mean QOL	85	48.9	24.4	53.5	0.0	97.0	
Treatment Mean QOL	85	86.4	15.0	92.0	39.4	100.0	
Treatment – Baseline Difference	85	37.5	28.8	36.1	-24.2	100.0	<0.0001
Percent Change over Baseline**	84	225%	536%	69%	-29%	3300%	<0.0001

Wagner I-QOL Part B - Modified Wagner Questionnaire	N	Mean	Std. Dev	Median	Minimum	Maximum	P-value*
Baseline Mean QOL	85	42.2	25.8	40.2	0.0	100.0	
Treatment Mean QOL	85	67.4	24.5	68.0	7.1	100.0	
Treatment – Baseline Difference	85	25.2	26.1	21.5	-22.3	90.8	<0.0001
Percent Change over Baseline**	84	157%	267%	54%	-45%	1383%	<0.0001

*Paired t test **Percent change not calculated if Baseline=0

- Mean scores improved by 25 points on inFlow (60%), statistically and clinically significant
 - Subjects were considered evaluable if they had both Baseline and Treatment QOL data
 - Based on within-subject QOL scores during Baseline (S1, B3, T1) and Treatment phases (T4, T7, T11, T16)
 - 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)

Comparative Safety: All Adverse Events

There were no unanticipated, serious or long-lasting adverse events

- As is common with urinary catheters, adverse events were frequent but minor
 - Rates generally decreased from the first half to the second half of Treatment phase, with the exception of bladder inflammation and all of those events were mild in severity

All Reported Events - Completers Only (n=77)	Baseline (Pt Months=179)		Treatment T1-T7 (Pt-Months=133)		Treatment T7-T16 (Pt-Months=189)		Treatment T1-T16 (Pt-Months=322)	
Adverse Event	Events	Rate	Events	Rate	Events	Rate	Events	Rate
Asymptomatic Bacteriuria	31	0.17	18	0.13	24	0.13	42	0.13
Bladder Inflammation	0	0	0	0	8	0.04	8	0.02
Frequency, Urgency, Bladder Spasms	10	0.06	13	0.10	7	0.04	20	0.06
Gastrointestinal Disorder	10	0.06	3	0.02	10	0.05	13	0.04
Genitourinary Pain	10	0.06	15	0.11	16	0.08	31	0.10
Hematuria / Scant Perineal Bleeding	1	0.01	3	0.02	4	0.02	7	0.02
Urinary Incontinence	14	0.08	40	0.30	37	0.20	77	0.24
Urinary Tract Infection	21	0.12	15	0.11	16	0.08	31	0.10
Vulvovaginal / <u>Periurethral</u> Disorders	11	0.06	12	0.09	10	0.05	22	0.07
Total, All Adverse Events	140	0.78	182	1.36	213	1.13	395	1.23

- Includes all occurrences of any adverse event during the specified period
- No statistically significant differences between Baseline and Treatment except genitourinary pain during T1-T7, bladder inflammation post T7 through T16, and urinary incontinence and all adverse events combined throughout Treatment
- Although based on Completers in order to compare study phases for the same set of subjects, safety profiles of subjects who dropped out did not differ in any clinically significant way from those who completed the study and thus provide no evidence of survivor bias

Comparative Safety: UTI Rate

The inFlow's UTI rate was lower than that for CIC

- *Indwelling* catheters are known to have an exceedingly high UTI rate compared to *intermittent* catheters, primarily due to the difference in device exposure times
 - As the inFlow is an indwelling device, its UTI rate was a prospective concern
- Instead, the inFlow's UTI rate started slightly lower than that for CIC and declined with continued use

Study Phase	Number Subjects	Total Patient Months	UTI Events	UTI Rate
Pivotal-Baseline (CIC)	77	179	21	0.12
Pivotal-Treatment T1-T7 (inFlow)	77	133	15	0.11
Pivotal-Treatment T7-T16 (inFlow)	77	189	16	0.08



- Based on Completers only in order to compare study phases with the same set of subjects
- Total UTI experience in pivotal trial = 157 subjects and 417 patient-months device exposure
- The Investigational Plan for IDE G970029 defined UTIs as marked by presentation of clinical symptoms in addition to urine analysis and so is consistent with current CDC recommendations
 - AB was also tracked as a leading indication, although high bacteria counts do not necessarily progress to UTI

Safety: Encrustation

No encrustation was reported

- Encrustation occurs in ~50% of patients with indwelling urinary catheters and along with UTI, is the most significant clinical problem associated with their use
 - Although a non-comparative measure, since inFlow is an indwelling device, encrustation rate was a prospective concern and so was tracked in the pivotal using a 4-point scale



- Following the pivotal, an *in vitro* study by Stickler showed inFlow's encrustation resistance to be **>8.4x superior** to an all-silicone Foley, the current gold standard:



*“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... (its) central lumen appeared to be essentially clear.”*



Summary of Pivotal Trial Results

Clinical Endpoints

Effectiveness

- Post-void residual
- Quality of life

Safety

- All Adverse Events
- UTI Rate
- Encrustation

All clinical endpoints were met or exceeded

- Almost 100% of subjects met the primary endpoint

- **Primary Endpoint:** Post-Void Residuals were Equivalent
 - 98% of subjects (113/115) met this endpoint – both inFlow and CIC were highly effective in emptying the bladder
- **Secondary Endpoint:** Quality of Life was Superior
 - The inFlow improved quality of life by 60% compared to CIC (clinically and statistically significant)

- All Adverse Events (AEs)
 - Comparable: No unanticipated, serious or long-lasting AEs
- UTI Rate
 - The inFlow's UTI rate was lower than that for CIC
- Encrustation
 - No encrustation was reported

- Actual device exposure time far exceeded prospective goal (2928 weeks vs. 1220 weeks)

Safety Profile

- The inFlow's pivotal trial showed it to have a favorable safety profile
 - No unanticipated, serious or lasting adverse events were reported
 - The inFlow's UTI rate was the same or better than that for *intermittent* catheters, an unprecedented finding for an *indwelling* device
 - There were no adverse tissue changes, as confirmed by cystoscopic examination - the device does not alter the anatomy
 - No device failed due to encrustation
 - Importantly, device could be easily and safely removed at any time, even by patients
 - Discomfort or leakage that resulted in dropout was promptly resolved with device removal
 - Also, although unfortunate, discomfort and leakage are clinically minor events and should not be confused with surgical complications
- The FDA's review of the safety data from the pivotal trial was the primary determinant in its decision to down-classify the inFlow from Class III to Class II
 - The inFlow became one of the FDA's first De Novo approvals

Supporting Clinical Studies

- Six non-comparative clinical studies (total $n=228$) with similar populations to the pivotal have been published in major peer-reviewed journals
 - Results were similar - no serious or lasting adverse events were reported, reported UTI rates were consistently low and best practice became better understood over time

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), <u>almost no device-related dropout</u> , 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.
<u>Schurch</u>	British Journal of Urology	18	Not Reported	Early study suffered from poor transition of a new technology to clinical practice and product quality issues.
<u>Nativ</u>	American Society for Artificial Internal Organs	17	0.03	<u>Nativ</u> 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.

Animal and Laboratory Testing

- The inFlow complies with ISO 10993:2013 standards for a surface device with permanent mucosal membrane contact and where applicable with ASTM and other recognized catheter standards

Test Type	Tests Conducted
Biocompatibility	<p>As the inFlow is classified 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:</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 additional 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>Per the FDA "The results of this testing support the biocompatibility of the inFlow device for its intended use."</p> <p>In 2016, 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	Complies with ISO 11137-2, Sterilization of Health Care Products - Radiation
Additional Applicable Standards*	<p>Laboratory tests 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 3 kHz to 300 GHz)
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 (11,552 operation cycles=5 years) • Activator Drop Testing (50 cm onto hard surface) • Activator Battery Endurance Testing (2 months)

* Not a complete list of tests conducted

Discussion of Device Acceptance

- Consistent with the prospective estimate, ~50% of pivotal subjects failed to complete the study for device-related reasons
 - Estimate was based on both prior clinical experience with the inFlow and reported acceptance rates for similar devices
- Women with IDC are a medically challenging population
 - Physiologically, their neurologic deficits can skew individual responses in a variety of ways
 - Psychologically, many are worn down by their primary medical condition and have little ability to deal with even small problems
- These factors make it difficult to predict their responses to the inFlow
 - 7 studies have failed to identify predictors of device success based on pathology or demographics
 - Motivation to persevere during the device accommodation period seems to be a key determinant
- Motivation is particularly hard to predict, but is easy to test
 - inFlow's pivotal trial showed that on-device trial could quickly identify those likely to be successful
 - No harm was done to those who failed (they simply resumed their prior catheterization method)
- User responses to the inFlow appear to be similar to those for contact lenses
 - In both cases, the most frequent reason for discontinuing use is discomfort, i.e. device awareness
 - In both cases, the simple answer is to try them and see (a quick go/no go)

Active Clinical Support

- Active clinical support has since been shown to increase device acceptance
 - Lynch *et al* provided pre-insertion medications, post-insertion nursing support, etc. and reported almost no device-related dropout in their 1-year study ($n=21$)
- **Pre-insertion:** Prophylactically account for typical responses to initial device use

The inFlow is a 24/7 foreign body in a sensitive part of the anatomy and a period of device awareness is normal (think contact lenses)	Set realistic expectations: Prior to insertion, advise patients they be uncomfortable initially, but let them know that any discomfort is likely to be temporary and benign. Depending on the state of the tissue surrounding the meatus, 30 day prep with an estrogen cream or OTC moisturizing gel (Restore™ or similar) can also be helpful.
Device also obstructs the urethra and the bladder's response to obstruction is urge, which can result in spasm or leakage	Prescribe appropriate medications: Consider a prophylactic course of anticholinergics starting 7-10 days prior to initial device insertion. MS patients may benefit from Botox in both the detrusor and bladder neck and other patients from Flomax.

- **Post-insertion:** Provide support for patients, particularly during initial device use

Patients will have questions and concerns	Establish a single point of contact in your practice: An experienced nurse can handle most issues
	Coaching works: Remind patients of device benefits to increase their motivation to persevere through the first 1-2 weeks while they accommodate to device
Communicate to patients that their care plan may require them to make behavioral changes	<ul style="list-style-type: none"> ○ Most Foley users have shrunken bladders and need to incrementally increase capacity via a timed voiding schedule with progressively longer intervals ○ CIC users often restrict fluid intake to limit the number of times they need to catheterize, but should now increase hydration

Risk/Benefit Summary

- The inFlow has been shown to have very little risk
- The inFlow is of significant benefit to those who can use it
 - Demonstrated effectiveness in emptying the bladder
 - Significantly improved quality of life compared to best currently available alternative
 - Lower UTI rate than current standard of care
 - 97.4% (75/77) of subjects who completed the Treatment phase of the inFlow's pivotal trial opted-in to continue using inFlow afterward
- Those likely to be successful can be easily, safely identified via on-device trial
 - Active clinical support has been shown to increase device acceptance

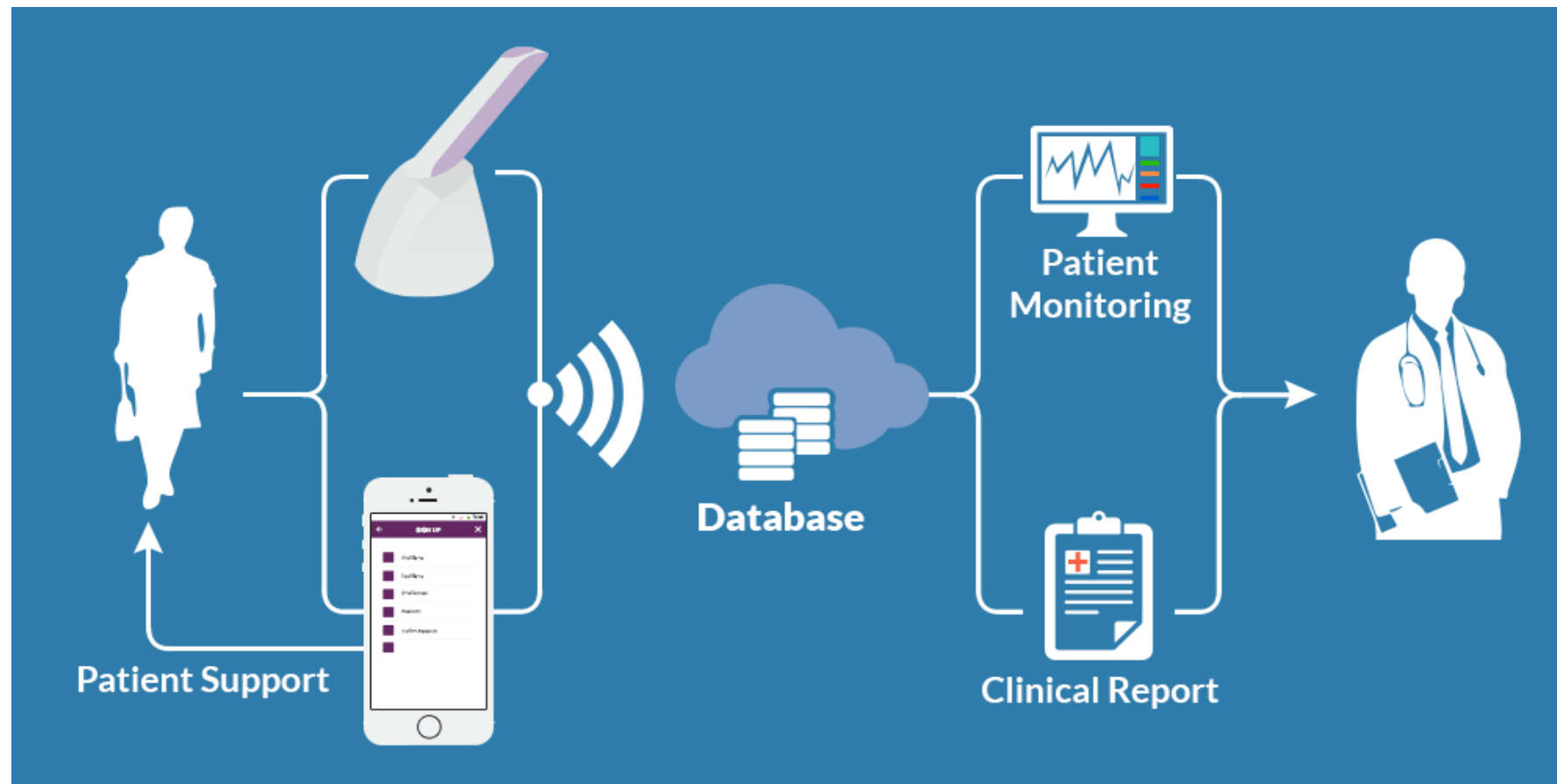
Presentation and Dossier



1. Burden of Illness
2. Product Information
3. Value Evidence Supporting Technology
4. Future Directions and Applications

The inFlow Voiding Care System™ (VCS)

- Active clinical support has been shown to increase the rate of successful inFlow use, but this may be considered too time-consuming by busy US urology practices
- In response, Vesiflo is developing a device-based mHealth condition management system intended to provide front-line support for prescribing urology practices



- The VCS is designed to identify problems interfering with successful device use as early as possible

Phase One: Compliance Monitoring

- New “smart” Activator can measure urine output each time device is used*
 - Low volume indicates likely compliance or health issues and warrants investigation



Each time its button is pressed,
Activator calculates urine output

Data are routinely transmitted
to our app and sent to cloud

No patient initiative is required

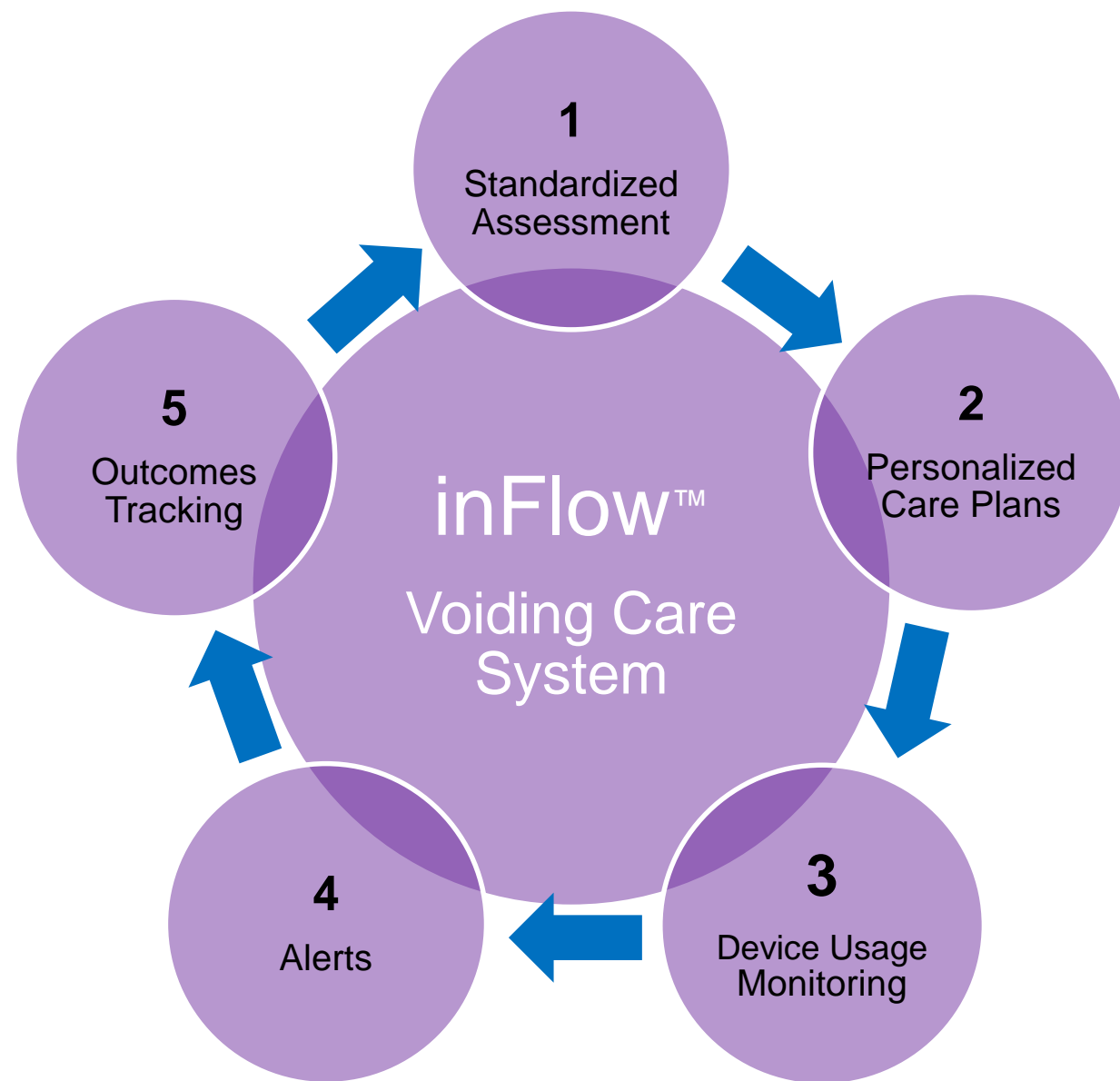
If urine output is low, clinician or
caregiver can be alerted



*USPNs 10,238,314 and 9,839,373

Note: This system is in development-stages
and is not being used clinically at this time

Phase Two: mHealth Condition Management



- 1. Standardized Assessment**
Online questionnaire to improve patient selection and assist in determining personalized care plans
- 2. Personalized Care Plans**
Clinical guidance and health coaching for patients, particularly during initial device use
- 3. Device Usage Monitoring**
Remote measurements of urine output
- 4. Alerts**
When urine output is low
- 5. Outcomes Tracking**
Outliers will be used to inform better methods for assessment and care plans

Thank You

“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

