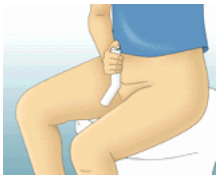
The In-Flow™ Female Catheter:
Summary of Clinical Evidence and Risk/Benefit Analysis

The In-Flow™ Female Catheter ("the In-Flow") is an indwelling urinary catheter that is designed to provide controlled bladder drainage. The In-Flow is similar to a Foley catheter in its method of insertion, anatomic location, patient contacting material and duration of use (29 days). It differs in that it uses a remote-controlled valve-pump mechanism to dynamically and completely empty the bladder. This eliminates tubes and collection bags and, as described in the next section, results in improved performance in areas where Foley catheters are known to be deficient.

The In-Flow catheter is inserted into the urethra similarly to a Foley or intermittent urinary catheter. It is typically inserted by a nurse or other caregiver, but can also be done by a trained user. To void, the user or her caregiver holds a remote control over the lower pelvic area and presses a button (right). This activates the pump, which rapidly drains the bladder. When the button is released, the valve is engaged, blocking further urine flow. Normal use is 29 days. The In-Flow can be easily and safely removed at any time, even by patients.



Preface: Key Clinical Issues

Urinary catheters, although widely used, are known to have significant problems, specifically a high rate of urinary tract infection (UTI) and low quality of life for their users. The U.S. IDE study (*n*=273) showed that the In-Flow has significantly improved performance in these areas:

- The In-Flow has a significantly lower UTI rate than any other indwelling catheter.

  Nosocomial (hospital-acquired) UTIs are estimated to affect 1,000,000 U.S. patients per year, resulting in 56,000 deaths (increasing with the emergence of resistant bacteria) and costing over $2 billion in direct medical costs. [1]

  The UTI rate for Foley catheters is well established: 5% risk of UTI per day (virtually 100% in 30 days). [2] The IDE study compared the In-Flow (also an *indwelling* catheter) to clean *intermittent* catheterization (CIC), the current standard of care for bladder drainage, and found that their UTI rates were directly comparable (22% of patients in the 8-week CIC phase and 22% of patients in the 16-week In-Flow phase). [3] In an ongoing follow-on study in which Canadian patients have continued to be followed under the IDE study protocol for over four years, Tu reports further, clinically significant reductions in the In-Flow's UTI rate starting after 6 months. [4]

- The In-Flow provides superior quality of life compared to any other type of urinary catheter.

  In the IDE study, the In-Flow improved quality of life by 50% compared to CIC, a difference that is both statistically and clinically significant. [3] In a study comparing it to a variety of catheterization methods, including other indwelling catheters, the In-Flow improved quality of life by 80%.[5]

  Improvements in quality of life are related to the following: a) The In-Flow eliminates tubes and bags, improving body image (as well as hygiene); b) It allows most patients to void without assistance, increasing self-reliance; and c) The In-Flow allows most patients to use a toilet again, a psychologically significant benefit since it is the "normal" way to void. The In-Flow's effect is described by family members of patients:

  "It can simply, yet absolutely transform the quality of individuals' lives."
  - Larry Coffee, Brother

  "…the device has been an unqualified success. It is difficult to put into words the effect that (the In-Flow) has had on (my daughter's) life."- E. Clark Buchi, Father

The In-Flow has been extensively studied. Clinical data are discussed in more detail in the document that follows.

At this time, there are five (5) clinical studies (total *n*=495) concerning use of the In-Flow catheter. In addition to the U.S. IDE study,[3] four independent clinical studies have been published in peer-reviewed journals.[5,6,7,8] A total of 52 patients from three studies were followed for at least one year. A summary of findings from these studies follows:

U.S. IDE Study

The IDE study (*n*=273) compared the In-Flow catheter to the current standard of care for bladder drainage, clean intermittent catheterization (CIC), for the treatment of women with acontractile (atonic) bladder. The results of the IDE study were unambiguous and positive:

- Primary endpoint: Post-void residuals (PVR). PVRs were equivalent. Over 95% of patients had PVRs while using the In-Flow that were comparable to those achieved while on CIC and over 95% of patients maintained PVRs of less than 50cc, with median PVR at each follow-up visit ranging from 10-20cc. PVRs for 95-100% of all patients were equivalent at every office visit.
- Secondary endpoint: Quality of life (as measured by the Wagner I-QOL, an incontinence-specific instrument). The In-Flow significantly improved quality of life compared to CIC. While using the In-Flow, patient scores for the Wagner IQOL improved by a mean of 25 points ($p<0.0001$), resulting in a 50% improvement, a difference that is both statistically and clinically significant.
- Safety: Comparative adverse events, particularly the rate of urinary tract infections (UTI). There was no significant difference in UTI rates associated with use of the In-Flow compared with CIC. UTIs were reported by 22% of patients during the 8-week baseline CIC phase and by 22% of patients during the 16-week In-Flow treatment phase. The numbers of episodes per person-month were similar between the two phases (0.125 versus 0.106) and this pattern continued into the post-treatment phase (0.110 episodes per person-month). Also, the In-Flow catheter caused no serious or lasting harm of any nature to any patient and cystoscopy data showed no significant damage to any patient's urethra at any time.

This study did report a high dropout rate, largely as a result of discomfort; however, its study protocol did not call for either patient disclosure of possible discomfort (which is typically temporary) or directed nursing support. No serious or lasting harm resulted and patients unable or unwilling to use the device simply resumed use of CIC. A more complete discussion of this issue can be found in the Risks section of this document.

In an ongoing follow-on to this study in which fifteen (15) Canadian patients have continued to be followed under the IDE study protocol for over four (4) years, Tu reports further, clinically significant reductions in the UTI rate starting after 6 months and no tissue changes found or cystoscopically revealed in annual exams. [4]

Independent Clinical Studies

Four (4) independent clinical studies (total *n*=222) report similar findings to the IDE study. No serious or lasting adverse events were reported and the most recent study reports improved device acceptance rates. Specific findings include:

- In the December 2003 British Journal of Urology, Lynch et al reported 80% improvement in quality of life and no negative tissue changes in their study of 20 atonic bladder patients after one year.[5] This study also reported a high rate of device acceptance (87%), which the authors attribute to: a) rigorous adherence to the known exclusion criteria and b) full disclosure of possible problems, including discomfort, followed by c) active nursing support.
- In an earlier study of 40 patients with voiding dysfunction (European Urology 2000), in which 21 patients were followed for more than a year with a follow-up time of 12-44 months (mean 24.6), Madjar et al concluded 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." [6]

To summarize clinical findings, the In-Flow functioned to provide drainage of the urinary bladder and its performance was as expected in all instances, with the exception that discomfort among atonic bladder patients was higher than anticipated and UTI rates were lower than anticipated. These issues are discussed further in the Risk/Benefit Analysis section.

Non-U.S. Clinical Use and Laboratory Testing

In addition to the formal studies cited, extensive clinical experience exists outside the U.S. The In-Flow catheter has been marketed in Europe for eight (8) years and over 10,000 devices have been sold (representing 833 women-years of use), with no significant adverse events reported to date.

As a CE-marked device, the In-Flow catheter conforms to Council Directive 93/42/EEC and its manufacture has been subject to annual inspections to confirm ISO compliance. In addition, comprehensive laboratory testing of the In-Flow has been conducted. Bench studies demonstrated that the In-Flow Catheter and Activator meet their performance specifications and, where applicable, conform to the requirements of relevant voluntary standards. Biocompatibility tests were also conducted to characterize the biocompatibility of the materials used in the In-Flow Catheter, Introducer, Activator, and Sizing Catheter. These tests demonstrated that these components do not cause cytotoxic response, irritation, or sensitization. The Catheter was also shown to be non-mutagenic.

A recent in vitro study by Stickler compared the performance of the In-Flow and a Foley catheter with regard to encrustation: "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 was still draining urine from the bladder model at 9 days, at which point the experiment was stopped. (Its) central lumen appeared to be essentially clear." [9]

Risk/Benefit Analysis

An analysis of risks and benefits based on the accumulated evidence follows:

1. Benefits for CIC users. The IDE study found that the In-Flow catheter improved quality of life (QOL) by 50% compared to CIC, while providing the same effectiveness as measured by comparative post-void residuals (PVR).[3]

   The improvement in QOL is made more impressive when considered in context: The IDE study involved only those women who were satisfactorily using CIC, i.e. higher-functioning patients who could perform the procedure themselves or who had a reliable caretaker willing to do it. This is not a group that might be expected to demonstrate a significant improvement in quality of life with an alternate method of bladder drainage.

2. Benefits for Foley catheter users. The UTI rate for the In-Flow, although an *indwelling* catheter, was directly comparable to clean *intermittent* catheterization (CIC), the current standard of care for bladder drainage (22% of patients in the 8-week CIC phase and 22% of patients in the 16-week In-Flow phase). [3] Since Foleys are known to result in 5% risk of infection per day, the IDE data show that the In-Flow will *reduce infection risk* for those who are unable or unwilling to use CIC.

   The In-Flow has additional benefits for patients who use Foleys on a chronic basis, specifically:

   - *Improved quality of life*. Lynch et al reported an 80% improvement in quality of life compared to alternative methods of bladder drainage.[5]
   - *Maintenance of bladder tone*. Prolonged use of Foleys causes the bladder to shrink and become non-compliant, and even short-term use can result in bladder dysfunction, particularly in elderly patients.[10] The In-Flow allows periodic filling and drainage of the bladder, which can promote tone and prevent shrinkage.

- *Maintenance of tissue integrity*. Long-term use of Foley catheters can result in patulous urethra. No clinically significant tissue damage associated with In-Flow use has ever been reported. Tu, Lynch, and Madjar confirm that even long-term use of In-Flow causes no harmful tissue changes.[4,5,6]

3. Risks: The IDE study reported that the In-Flow was equivalent to CIC in terms of the rate of UTI. Other adverse events were similar, with the exception of discomfort and incontinence, which were more common with the In-Flow. In general, adverse events associated with the In-Flow were of mild severity and were resolved quickly with device removal. No significant tissue damage associated with In-Flow use has been reported or cystoscopically observed in any patient, either by the IDE or its ongoing follow-on study. In fact, there is no report of any serious or lasting harm to any patient at any time related to use of the In-Flow.

   Certain concerns that seemed plausible prior to formal study and extensive clinical use (specifically tissue erosion, inadvertent valve opening due to localized magnetic force, and unintentional obstruction) have been proven not to result in adverse events:

   - Clinical studies by Tu, Lynch, and Madjar confirm that long-term use of the In-Flow causes no harmful tissue changes.[4,5,6] In fact, Lynch reports that it can even provide beneficial changes in patients with compromised tissue (patulous urethra) related to long-term use of Foley catheters.[5]
   - The In-Flow magnetic valve is designed to be activated by a rotational magnetic field (versus a standard static magnetic field), thus making it almost impossible for the valve to be environmentally affected. Extensive laboratory testing has confirmed that inadvertent magnetic release of the valve and subsequent uncontrolled loss of urine are highly unlikely to occur except with deliberate effort. Also, there were no reports of accidental activation in the IDE study or any other clinical study.
   - The In-Flow has proven to be safe with regard to unintentional obstruction. The IDE study reported that patients leaked around the device (which is possible due to the lack of a balloon at the bladder neck) and there have been no reports of complications such as vesicoureteral reflux and hydronephrosis in the IDE or any other clinical study (total n=495) or in eight years of non-U.S. use involving over 10,000 devices sold.

   As stated previously, the IDE study reported a lower rate of device acceptance than anticipated,[a] due largely to device awareness/discomfort; however, its study protocol did not call for either patient disclosure of possible discomfort (which is typically temporary) or directed nursing support.[3] In retrospect, the failure to fully account for the issue of device accommodation in the IDE study protocol seems like an obvious oversight, particularly since this study was limited to women who were satisfactorily using CIC, which by definition contacts tissue only intermittently; whereas the In-Flow is an indwelling catheter and remains in place for 29 days. A recently published study by Lynch et al reported a high rate of device acceptance (87%),[5] which the investigators attribute to a protocol that included patient education and active nursing support.[b] This reaffirms the conclusion reached by IDE Clinical Investigators Tu and Kennelly, who stated in their post-IDE analysis that "Our experience has shown that patient selection, education and support are crucial to successful device acclimatization…"[3] Accordingly, the manufacturer of the In-Flow, SRS Medical, has revised the *Physician Instructions for Use* that accompany each device and now provides specific advice to this effect (excerpted here):

   > NOTE: For some patients, use of the In-Flow Catheter entails a period of accommodation similar to that required for contact lenses. Inform patients that this may occur and instruct them to contact you or your nurse immediately if they are concerned about the level of their discomfort. Most patients who experience discomfort find that it is temporary (lasting 3-5 days) and can be palliated with pain relievers and hot baths.

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[a] The In-Flow device acceptance rate, which was initially only 39% of IDE subjects, subsequently increased to 61% following a revision of the study protocol in which a trial period was added. No instructions regarding device accommodation were ever provided.

[b] Personal correspondence with Clinical Investigator.

> Follow-up calls by nurses are crucial to appropriately identify any problems and to reassure patients, particularly if they experience discomfort during the accommodation period. Suggested points of contact are about 12 hours after the initial insertion of the device, and further phone follow-up within the first week.

Notwithstanding its effect in limiting device candidates, this secondary adverse event is clinically minor in nature; that is, no serious or lasting harm was ever associated with the complaint of patient discomfort. (In the IDE study, patients unable or unwilling to use the In-Flow simply resumed use of CIC.[c]) Also, unlike Foley catheters, the In-Flow can be easily and safely removed at any time, even by patients. Therefore, the manufacturer's revised physician instructions are likely to prove an adequate remedy.

The weight of evidence supports the conclusion that the risk/benefit for the In-Flow catheter is overwhelmingly favorable:

- For patients able to tolerate the In-Flow, it significantly improves their quality of life while providing them with safety and effectiveness comparable to CIC.
- For patients unable to tolerate the In-Flow, no serious or lasting harm is done.

Summary

Clinical data to date, including long-term data, indicates that the In-Flow female catheter is a safe and effective alternative for chronic catheterization, an area of acute need. Although the In-Flow is not suited to all female patients requiring catheterization, it can provide safe, convenient and dignified bladder drainage for a number of patients, significantly improving their quality of life and, in the case of patients who would otherwise use Foley catheters, substantially reducing their risk of UTI.

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[c] Discomfort did not have a meaningful clinical impact on patients who were able to use the In-Flow, as demonstrated by the statistically significant difference in I-QOL scores in In-Flow treatment arm subjects as compared to CIC baseline arm subjects.