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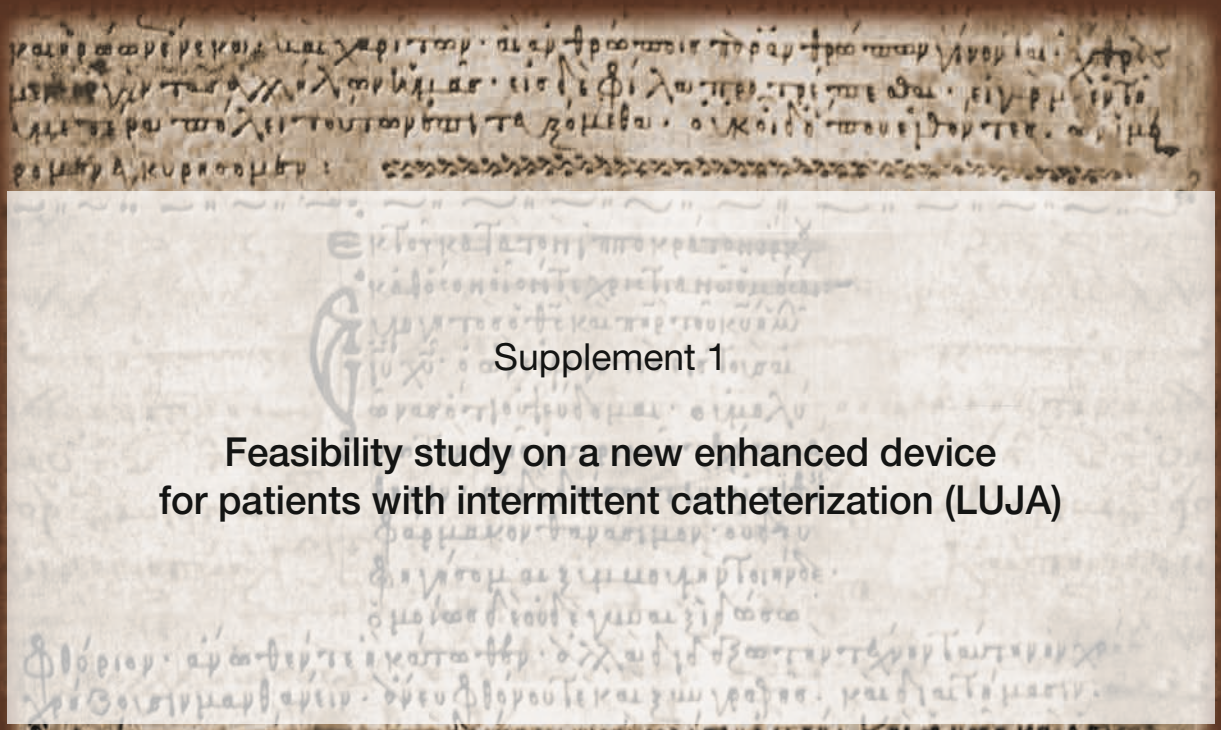

Supplement 1

# Feasibility study on a new enhanced device for patients with intermittent catheterization (LUJA)

The original document of Hippocrates' oath

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# Feasibility study on a new enhanced device for patients with intermittent catheterization (LUJA)

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# LUJA Project (Background, Project aim, Project structure and main contents, Materials and methods)

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## Background

Intermittent catheterization (IC) has been part of the therapeutic arsenal for urinary retention problems for several thousands of years. It is used in current clinical practice to manage urinary retention problems of neurological or non-neurological origin [1-5]. The procedure is recommended by numerous learned societies for the management of neurogenic bladder disorders and it is considered as the gold standard for the management of voiding dysfunction. However, there is no clear international consensus on IC indications, on training modalities, equipment to be used, implementation modalities, screening and infection management, modalities of third-party catheterization and IC in specific populations such as children, the elderly, urinary diversion patients with continent cutaneous reservoirs or benign prostatic hyperplasia patients (BPH). This is creating disparities between practices and may restrict patients' therapeutic options.

Recently, the European Association of Urology (EAU) Neuro-Urology Guidelines reported that IC is the standard treatment for patients who are unable to empty their bladder. Therefore, the Experts recommended the use of IC, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder [6].

In addition, the results of a French consensus on IC were published [7]. In these French guidelines, four different conditions were defined: Short-term bladder drainage; Long-term bladder drainage; Bladder emptying in neurological disorder patients; Urinary retention in BPH. Insufficient and very heterogeneous data have emerged from the evidence of this scientific research, which focused on evaluating the optimum method for the four conditions included in the assessment.

However, in the case of urinary retention due to BPH, it has been shown that IC for a period of 6 months, prior to BPH surgery, is more effective for recovering post-operative bladder function when compared to BPH surgery alone [8]. This was a randomised study of 41 BPH patients with a PVR greater than 300 ml. Patients were randomised into two groups: one group underwent Trans Urethral Resection of the Prostate (TURP) (n = 17) and the other group underwent IC for a period of 6 months prior to surgical treatment. At 6 months post-surgery, i.e. after both groups of patients had undergone TURP, quality of life and IPSS scores improved in both groups, but the group of patients undergoing IC for 6 months prior to TURP had better bladder drainage, as shown from their pressure-flow curves.

An underactive bladder muscle, bladder outlet obstruction or a combination of both may cause urinary retention. Independent of underlying mechanisms, not only cause incomplete bladder emptying, worsening storage symptoms such as frequency, nocturia, urgency and incontinence, but it may also predispose patients to a wide range of complications, including recurrent urinary tract infections (UTIs), bladder stones, upper urinary tract changes and even renal impairment [9].

Catheter-associated urinary tract infections (CAUTIs) are one of the most common nosocomial infections and can lead to numerous medical complications from mild catheter encrustation and bladder stones to severe septicaemia, endotoxic shock, and pyelonephritis.

Catheters are one of the most commonly used medical devices in the world and can be identified as either indwelling (ID) or intermittent catheters (IC). The primary challenges in the use of IDs are biofilm formation and encrustation. ICs are increasingly seen as a solution to the complications caused by IDs as ICs pose no risk of biofilm formation due to their short time in the body and a lower risk of bladder stone formation. Research on IDs has focused on the use of antimicrobial and antibiofilm compounds, while research on ICs has focused on preventing bacteria entering the urinary tract or being exposed to the catheter [10].

Over the years, in addition to a greater risk of infection associated with catheterization, a hypothetical correlation has emerged from the scientific literature, especially in the case of permanent catheterization, with a greater risk of inflammation and histological changes of the bladder mucosa [11-13].

Therefore, some researchers argue that, according to this hypothesis, IC should be recommended in order to minimise adverse histological changes in the mucosa of bladder, as it does not require the use of chronic indwelling catheters [12].

The clean intermittent catheterization (CIC) is a preferential intervention for urinary retention in the clinical practice in Italy; it is chosen based on patient's characteristics, and lubrification, usability and easy insertion are the most important features of catheters [14].

The clinical conditions associated with the use of catheterization have a potential negative impact on health-related quality of life, and the associated economic costs can be overwhelming for patients and for the healthcare system. Indeed, healthcare usage may be excessive for these patients, including emergency department visits and subsequent hospitalisations [15].
In Italy, single-use catheters are considered the standard method for IC, and four catheters per day are delivered to users by local health agencies.
In addition to the risk of UTIs, performing IC several times a day represents a risk for urethral trauma. The latter can occur with or without the presence of haematuria and is associated with an increased risk of UTIs [16, 17]. A catheter reducing the risks of urethral trauma and/or UTIs may limit the economic burden for the healthcare system and may increase the quality of life for patients.
A recently published study [18] aimed to perform a cost-effectiveness analysis (CEA) from an Italian Healthcare Service perspective, comparing the two most frequently used catheter types for IC (i.e., disposable hydrophilic coated or uncoated plastic catheters). This was done to add value to previously conflicting results of CEAs evaluating different catheter types, and to identify the most cost-effective catheter alternative for the Italian setting.
A budget impact analysis (BIA) was also conducted to evaluate the impact on the Italian healthcare budget of IC for the management of bladder dysfunctions over a period of 5 years.
The base-case ICER and ICUR associated with hydrophilic-coated catheters were € 20.761 and € 24.405, respectively. This implies that hydrophilic-coated catheters are likely to be cost-effective in comparison to uncoated ones, as proposed Italian threshold values range between € 25.000 and € 66.400. Considering a market share at year 5 of 89% hydrophilic catheters and 11% uncoated catheters, the additional cost for Italy is approximately € 12 million in the next 5 years. Considered over a lifetime, hydrophilic-coated catheters are potentially a cost-effective choice in comparison to uncoated ones. These findings can support policymakers in evaluating IC in the target population of the study (patients with spinal cord injury). However, the findings of this study are limited to costs from a healthcare perspective. A broader evaluation, also including costs from a societal perspective, would increase the understanding of the economic sustainability of these devices.
A systematic review on the cost-effectiveness of hydrophilic-coated urinary catheters for individuals with spinal cord injury was recently published [19]. The search identified 371 studies, of which eight studies met the inclusion criteria. Five studies observed hydrophilic-coated catheters to be cost-effective compared to uncoated catheters. Two studies found hydrophilic-coated catheters to be not cost-effective compared to uncoated catheters and one study estimated that hydrophilic-coated catheters reduced the long-term health-care costs compared to uncoated catheters. In conclusion, the cost-effectiveness of hydrophilic-coated catheters was dependent on the comparator used, the consideration of long-term effects, and the unit cost of treatment. Further studies are needed to explore the short-term and long-term effects of hydrophilic-coated catheter use on urinary tract infections and clarify the impact of hydrophilic-coated catheter use on long-term renal function. Overall, the critical evaluation of the literature suggested that the evidence is pointing toward hydrophilic-coated catheters being cost-effective, particularly when a societal perspective is applied.
Many questions are still unanswered about IC and its clinical indications. What is the underlying disease treated with IC most associated with urinary tract infection? Which type of catheter is mostly associated with infections? What is the risk of bladder mucosal injury associated with IC? Is there a significant difference in terms of cost or convenience for patients and hospitals in relation to the device used and the type of catheterization? We still need more and better scientific evidence on these open points in order to ensure an adequate and value-based healthcare offer to our patients.

## Project aim

The project aimed to carry out a feasibility study to investigate the characteristics of the target population (adult population with spinal cord injury) and the clinical and economic burden of IC with a particular focus on urinary tract infections complications and related costs. Particular attention was paid to the use of IC in BPH (in men) and multiple sclerosis (in women). In this feasibility study, the use of the new enhanced device of Coloplast (Luja) was evaluated to define its strengths and weaknesses in the management of patients with IC from a value-based perspective.

## Structure of the project and main contents

The project was developed through four phases:
- Phase I: research of scientific evidence;
- Phase II: economic model processing;
- Phase III: assessment phase;
- Phase IV: technical report drafting.

### Research of scientific evidence

This phase attempted to reach the following objectives:
1. to identify the target population and its main characteristics;
2. to stratify patients in relation to the pathology treated with IC;
3. to identify the clinical and epidemiological burden of the main IC-related complications;
4. to research scientific evidence on economic burden of IC complications;
5. to assess the main features of Luja and the Italian regulation context in relation to the introduction of the new technology being evaluated.

### Economic model processing

This evaluation is based on the adaptation to the Italian context of a model developed by the health economics consortium of the University of York (YHEC). The adaptation process involved finding sources, tariffs, DRGs, drug acquisition prices, epidemiological data from the Italian context. In particular, the evaluation detailed in this report is in a population of MS and SCI individuals using ICs and takes a National Health Service (NHS) perspective, in the Italian setting.

### Assessment phase

The third phase of this project aimed to pursue the following objectives:

- to share the results of the previous phases with an expert panel in order to identify the necessary steps to register the new device in the Italian setting and to evaluate the main items to consider to perform an HTA of the new device.

### Technical report drafting

The last phase of the project was the drafting of the final technical report, which collects the main results obtained based on scientific evidence and experts' opinion.

## Materials and methods (tasks)

In order to reach the objectives the work plan consisted in the following phases and tasks.

### Research of scientific evidence

Systematic reviews of existing literature were performed in order to provide an overview of the current and potential impact of the use of the new Luja device within the Italian context. Evidence were selected in accordance with pre-defined inclusion criteria and summarized based on the Health Technology Assessment (HTA) domains under the framework of the European Network for Health Technology Assessment (EuNetHTA) Core Model® (www.eunethta.eu).

The following activities were conducted to achieve the objectives related to this phase:

- construction of a PICO model to set the PubMed search;
- identification of the keywords to be included in the search string;
- selection of the articles based on previously defined inclusion criteria;
- systematization of scientific evidence.

### Economic model processing

One of the aims of this feasibility study was to structure an economic model, focused on the Italian healthcare setting, trying to assess the potential cost savings derived by less resource utilization in the treatment of infectious and inflammatory complications related to the use of IC. Hence, a systematic review was structured querying the main scientific databases in order to collect useful information to develop the model. In particular, the research was focused on estimating the costs of the main complications linked to the target population in the Italian healthcare setting. Once we will find relevant information about the management and costs associated with these complications, a model was structured and a sensitivity analysis was carried out on the potential efficacy in reducing infectious and inflammatory IC-related complications utilizing the catheters currently available. For this activity, a Global model of Coloplast was used.

### Assessment phase

According to the HTA approach, an expert advisory board was established with the aim of providing expertise for the integration of evidence coming from the existing literature.

### Technical report drafting

The final project document was drawn up based on scientific evidence and expert feedback.

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Chapter 1

# Research of scientific evidence on clinical and epidemiological burden of complications related to intermittent catheterization

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## Introduction

### Intermittent catheterization: historical data

Catheterization is probably one of the oldest surgical procedures dating all the way back to 3000 years before Christ. The ancient Egyptians used to have catheters from bronze, but gradually they introduced those of gold, and even the wood ones. In the mid-1930s, the American urologist F. Foley introduced the first balloon catheter – the Foley catheter [1].
In 1947, Guttman introduced the concept of sterile intermittent catheterization (natural desideratum from a principial point of view for every medical step, but difficult to apply especially in conditions of catheters technical performance in that époque). In 1966, Guttman and Frankel presented the first long-term study about sterile intermittent catheterization [2]. Based on it and on an almost 7 decades of clinical practical use, intermittent catheterization (IC) has been validated and accepted as the state of the art in management of neurogenic bladder emptying disorders, in spinal cord injured people being lifesaving by reducing the risk of urosepsis and renal deterioration [3].
In 1972, Lapides introduced the concept of "clean intermittent catheterization" (CIC) as an important contribution in IC, which meant a revolutionary improvement in the neurogenic bladder management. In the beginning, IC was performed with polyvinyl chloride (PVC) catheters later replaced by some low-friction catheters to reduce catheter-related complications [4].

### Clinical conditions and intervention description

Many people, including those with neurologic deficits, urethral obstruction from strictures or tumors, or bladder dysfunction post-surgery, experience chronic incomplete bladder emptying. It occurs when the muscles of the bladder do not squeeze sufficiently to empty the bladder itself. When this happens, an artificial means of draining the bladder is needed. IC has become widely established during the last decades as the gold standard for the management of neurogenic lower urinary tract dysfunction (NLUTD). IC can be performed by patients of different age groups, including the very elderly and children starting from 4 years old under parental supervision and careers [5].
In IC, the catheter is passed through the urethra (or occasionally another catheterisable channel such as a Mitrofanoff continent urinary diversion, a surgically constructed passage connecting the bladder with the abdominal surface) into the bladder, and urine is drained as needed. The catheter is removed immediately after urine drainage until the next void is necessary. Alternatives to IC include suprapubic pressure (Credé manoeuvre) or an indwelling catheter, which is left in place for a period of time.
Fundamental to assessing suitability for IC users are impact on quality of life, frequency-volume charts, functional bladder capacity, post-void residual urine and urodynamics. A post-voiding residue > 100 mL is considered significant, and the practice of IC is recommended above this threshold [6]. Clinical decisions are also informed by urodynamic findings, detrusor pressures on filling, presence of vesical/ureteral reflux and renal function for both the adult and pediatric populations. Catheterization frequency should be based on individual care plans, typically performed four to seven times a day, like a normal adult voiding routine [7].
There are few data reporting the number of people using intermittent catheters globally, but it is estimated that there are over 300.000 users in the USA alone [8].

### Different catheters and techniques

*Techniques: aseptic versus clean*

IC can be carried out with sterile (non-touch) technique as originally proposed by *Guttmann and Frankel* [2]. It involves the use of sterile gloves, a sterile single-use catheter, disinfection or cleansing of the genitals and use of sterile lubricant if the catheter is not pre-lubricated. This aseptic technique, mainly used by healthcare professionals in hospital settings, minimize the risk of introducing pathogenic microorganisms during catheterization and thereby reduce urinary tract infections (UTIs) and/or bacteriuria when compared with clean techniques. The latter, described by Lapides et al. (1974) in 1970, involves using either a sterile single-use catheter or a clean reused catheter and a clean container with clean gloves or hand washed with soap and water. This technique is less time consuming, decreases the cost of

IC and improves quality of life [9]. A clean technique is used for intermittent self-catheterization (ISC), where a sterile or clean (multiple use) catheter is inserted with clean, ungloved hands and with or without a cleansing solution (soap and water, or water alone) and clean or sterile lubricant.

*Design: uncoated versus hydrophilic-coated*

Plain uncoated polyvinyl chloride (PVC) catheters (typically clear plastic) are loaded individually in sterile packaging. They may be supplied pre-lubricated, used with a separate lubricant or with just water to aid insertion. PVC catheters are used routinely multiple times because of expenses or environmental burden.
Coated catheters are single-use only and are designed to enhance catheter lubrication and facilitate ease of insertion with an aim reduce urethral trauma and risk of UTIs. The most prevalent coatings are hydrophilic, which necessitate the addition of water to the catheter to develop a lubricious layer, or pre-lubricated whereby the catheter is supplied prepackaged with a layer of water-soluble gel [10]. Hydrophilic-coated catheters are typically PVC, have a bonded coating and are packed individually in sterile packaging. The aim of hydrophilic-coated catheters is to reduce friction and, therefore, reduce trauma and infection. Most common hydrophilic-coated catheters are either supplied ready to use or require the addition of water at the time of use to form a lubricious layer.

*Strategies: single-use versus multiple-use*

Single-use catheters are used once before disposal. Multiple-use catheters are cleaned with detergent and water or disinfected by boiling, microwaving, or immersing in chemical disinfectant between uses. They may be reused a varying number of times (e.g., for up to 24 hours or for one week). We use the term 'multiple-use' to mean catheters that are used multiple times in the studies.
There are two major safety concerns with reusing catheters intended for single use. First is the cleanliness and sterility of the catheter and the subsequent risk of genital urinary tract infection (UTI) due to inappropriate cleaning and re-sterilization [11]. Second is the effect of cleaning and sterilization on the physical properties of the catheter material [12].

## Possible complications

Although it has fewer complications than those associated with an indwelling catheter [6], persistent or recurrent UTI is a common complication of IC [13, 14]. Other complications include prostatitis, epididymitis, urethritis, urethral strictures, and false passage. Urethral irritation, measured by haematuria, is reported particularly when intermittent catheterization starts but is not reported as being long-lasting [13, 14].

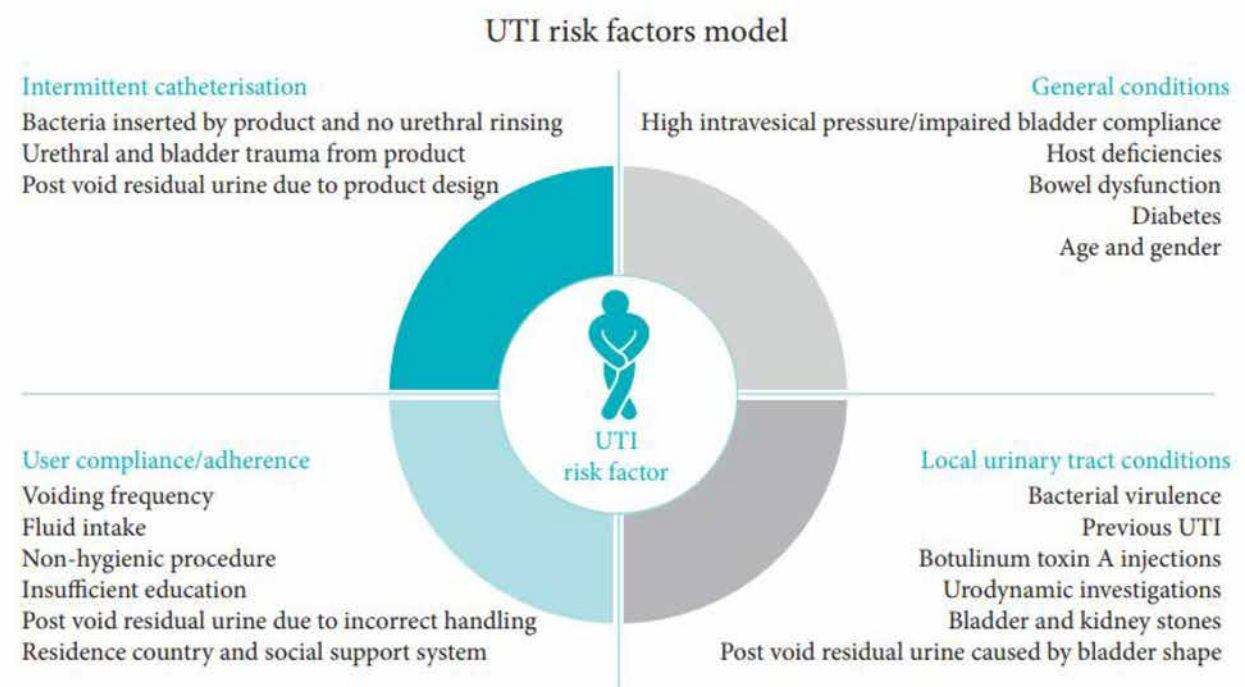
*UTIs*

The correct use of IC and strict compliance with hygiene instructions should avoid negative effects of continuous long-term catheterization; however, a major complication of catheterization is still the increased risk of developing a UTI [13], which can result in bacteremia/sepsis. To counteract and/or prevent UTIs, a common therapy is antibiotics, which are prescribed for acute and prophylactic use [15].
By the way, Angermund et al. (2021) [16] found out that UTIs also decreased over time after starting catheterization, suggesting that IC utilization and practice may have a positive influence on UTIs onset.
Moreover, as anticipated, reuse of clean catheters could be a reason for UTIs onset in managing patients with chronic urinary retention [14]. In a recent literature review [17] single use of catheters in adults (hydrophilic-coated or uncoated) was unanimously considered to impose a lower risk of UTIs. In fact, reuse of catheters exposes the patient to a plethora of possible cleaning techniques and duration of catheter use. Patient adherence to cleaning method cannot be predicted and this further amplifies the risk of complications and their burden on the healthcare system.
In 2019, Kennelly and Colleagues developed a risk factor model for UTIs in patients with adult neurogenic lower urinary tract dysfunction performing clean IC [18]. This model consists of four domains (Fig. 1), namely, (1) general (systemic) conditions in the patient; (2) individual urinary tract conditions in the patient; (3) routine aspects related to the patient, and (4) factors related to intermittent catheters *per se*. The conceptual model primarily concerns patients with spinal cord injury, spina bifida, multiple sclerosis, or cauda equina where IC is a normal part of the bladder management.
Authors concluded that there is a need for alignment of the definition and diagnosis of UTIs. It may be done disease per disease or more generally. Moreover, there is a paucity of evidence describing the UTI risk profile, and well-designed clinical trials are warranted to provide the clinician a better platform for adequate management of the UTI risk profile to the benefit of these patients. Guidelines, when available, should be adhered to, but they are not such clear (*see below*).

## IC: International Guidelines and target population

Re-use of catheters for the purpose of IC has been popular and widely used, being practiced by more than 35% of patients in North America [19]. Despite this common use, the evidence on the prevalence of UTIs associated with repeated use of a catheter is conflicting [20, 21].
Aside from questionable cleaning methods, it is unclear how long a multiple-use catheter can be reused. With the level of variation observed across clinical trials, it is likely that similar, if not more variation can be expected in public use. The lack of evidence-based recommendations is sure to confuse the public and alter their adherence to cleaning methods [11].
The American Urological Association (AUA) white paper on catheter-associated UTIs provides no recommendation on cleaning the reusable catheters, stating that hydrophilic-coated catheters may be preferable to standard uncoated ones [22].

Fig. 1. The UTI risk factors model with its four domains [18].




The European Association of Urology (EAU) recommends aseptic IC for patients with neurogenic bowel [23]. Given the difficulty of completely sterilizing catheters at home and considering the challenge of keeping the sterility with reusable catheters, specifically for neurologically impaired patients, single-use catheters remain the only realistic option.

The same way, Society of Urologic Nurses, and Associates (SUNA) specifically recommends that a new catheter be used for each catheterization [24]. The European Association of Urology Nurses (EAUN) states that the gold standard remains a single-use sterile catheter and highlights concerns about the cleaning efficacy and compliance associated with multiple-use catheters [25].

As of 2020, the Canadian Urological Association (CUA) recommends single use intermittent catheters, ideally those that are hydrophilic or pre-lubricated [26]. In fact, Canadian nurses no longer support the re-use of intermittent catheters at all.

We can conclude that single-use and re-use intermittent catheters should be safe the same way if modality of sterilization and times of re-utilization have been accurately defined by International Guidelines. The lack of coherence and detailed formation and/or information about it, seems pushing to trust more of single-use catheters.

About the theme of eligibility population, International Guidelines recommend intermittent catheters use to manage chronic urinary retention, in general. There is, however, no clear consensus and there are currently no national or international guidelines on indications, which necessitate intermittent catheterization.

What it is sure is that bladder emptying dysfunction, and consequently urinary retention, can occur in patients with neurological and non-neurological causes [23, 27-30].

Among neurological causes, it is mandatory to know that any events or conditions can damage nerves and nerve pathways resulting in a neurogenic bladder. Some of the most common causes are spinal cord injury, multiple sclerosis, spina bifida, Parkinson's disease, stroke, diabetic neuropathy etc.

With attention to non-neurological causes, it can be mentioned benign prostatic hyperplasia (BPH), post-operative urinary retention, idiopathic detrusor underactivity and refractory bladder (caused by urethral obstruction due to infection, metastases, or congenital abnormalities).

Thus, international guidelines recommend IC for people with bladder emptying dysfunction. However, there is no clear consensus and there are currently no national or international guidelines on indications that necessitate IC.

## Clinical and epidemiological burden of complications related to intermittent catheterization

In order to achieve the aim of this research a literature review was performed.

### Methods

*Definition of the research question*

The Table I summarizes the PICO model underlying this research, including the population under study (P), the

Tab. I. PICO model.

| | |
|---|---|
| Population | Adults with intermittent catheterization |
| Intervention | Intermittent catheterization |
| Comparator | - |
| Outcome | Clinical and epidemiological burden of IC complications |

intervention being assessed (I), comparator (C), and outcomes of interest (O).

*Search strategy*

A systematic review of the literature was performed and reported according to the *Preferred Reporting Items for Systematic Reviews (PRISMA)* [31]. Studies have been included according to stated inclusion and exclusion criteria. Three researchers have carried out title/abstract screening and the selection of the studies independently. The systematic research was conducted between November 2021 and December 2021 through PubMed and Web of Science databases with the established search strings (Tab. II).

*Inclusion/exclusion criteria*

All studies focused on the clinical and epidemiological burden of IC-related complications in the adult population were considered as potentially eligible. Original articles and systematic reviews published between 2012 and 2021 were selected, written in English language, and containing pertinent keywords in the title and/or abstract. Articles including pediatric population and including only other types of catheterizations were excluded. Narrative reviews, commentary, editorials, conference presentation and abstract not provided with full text were not included as well as studies conducted in animals or in vitro.

Thus, records retrieved through the search strategy were considered eligible unless they met one or more of the following exclusion criteria:

- not relevant to the condition under study;
- not English language;
- not sufficient information on any of the aspects under study;
- not full text;
- not adult population.

*Selection process and data extraction*

The selection of articles followed the criteria defined in the PRISMA Statement and was independently performed by two researchers (F.D'A and F.O.). Any disagreement was resolved by discussion or by the involvement of a senior researcher (G.E.C.).

Records retrieved where classified into an Excel worksheet containing for each record the database in which it was found, indication of whether it was a duplicate or not, first author, title, journal, year of publication, a drop-down menu indicated whether it was to be included or excluded, reasons of exclusion, note and name of the reviewer who selected it.

From the articles definitively included in the literature review, the following data were extracted by the researchers and summarized in two tables: first author's name, publication year, country, objective of the study, study design, characteristics of the target population, pathology treated with IC, characteristics of catheters, complications details and main findings related to the clinical and epidemiological burden of IC related complications.

When included, the systematic reviews were subjected to the snowballing process, evaluating their reference lists and citations in order to identify further articles that met the inclusion criteria of this review.

## Results

The database search, after duplicates removal, brought a total of 7.165 records. The first selection was carried out, initially, with analysis by title and abstract and 118 full texts were chosen to read. Following the inclusion and exclusion criteria pre-established for the study, the screening resulted in the final inclusion of 37 articles. Details about the study selection process are reported in Figure 2.

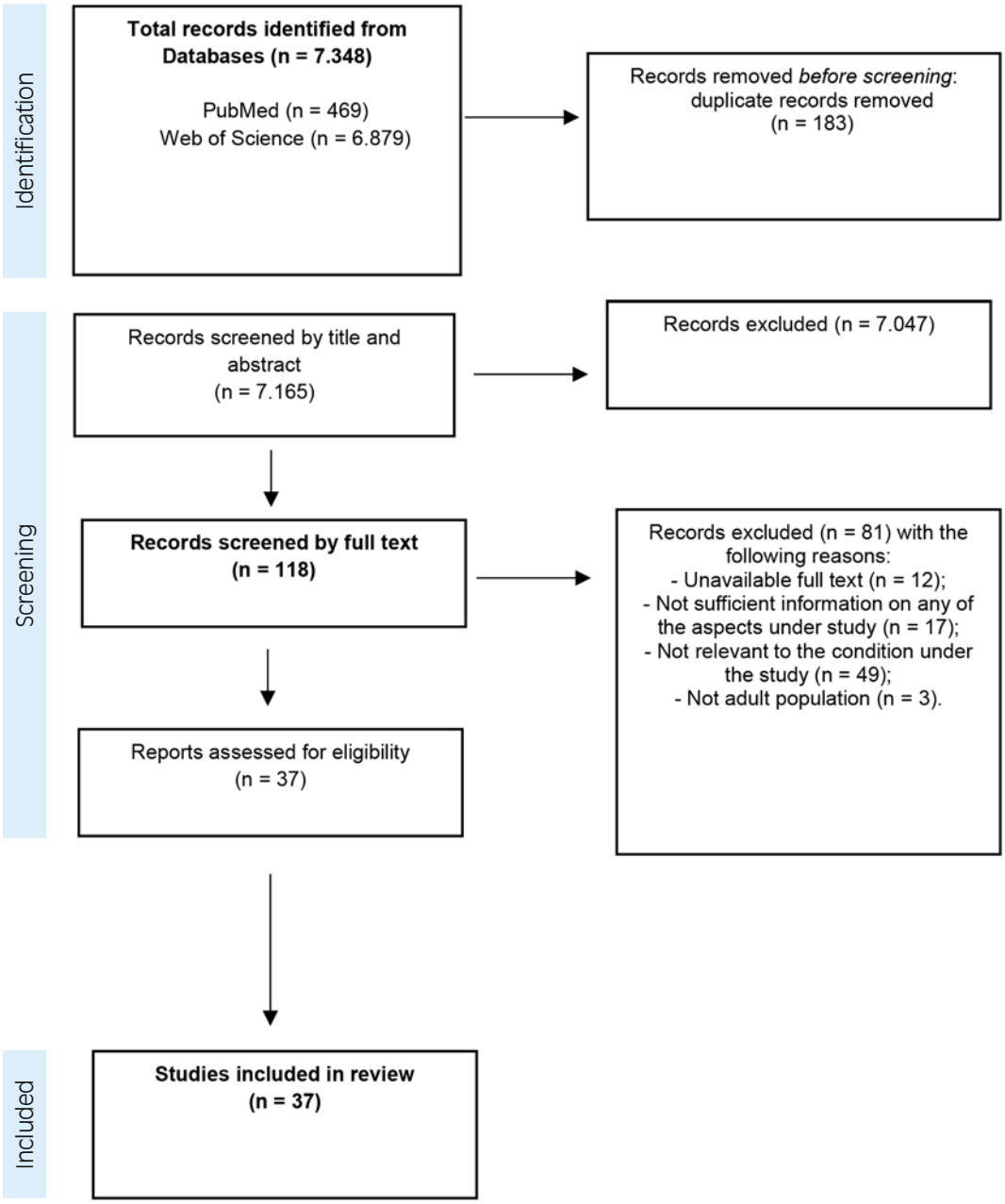
The studies were conducted in multiple countries, used a variety of research designs, and focused on different target population.

The study types included 11 reviews (30%) (eight systematic reviews, two literature reviews, one scoping review) [20, 32-41], and 26 primary studies (18 longitudinal studies (49%), five cross-sectional studies (13%) and three trials (8%)) [42-67] (Tab. III). Therefore, to be methodologically consistent, the reviews were analyzed separately, and the results are presented in Table IV.

Tab. II. Search strings.

| Database | Search strings | Filters | N. of articles |
|---|---|---|---|
| PubMed | ((((Intermittent[All Fields] AND ("catheterization"[All Fields] OR "catheterization"[MeSH Terms] OR "catheterization"[All Fields]))))) AND ("complication*") | Last 10 years, Humans, English, Medline, Adult: 19+ years | 469 |
| Web of Science | (((ALL=("intermittent")) AND ALL=("catheterization")) OR ALL=("catheterization")) AND ALL=("complication*") | Last 10 years, English | 6,879 |

Fig. 2. Study selection process (PRISMA flow diagram).




The articles were published between 2012 and 2021. None of the studies was performed in Italy, as they were conducted in USA (n = 7), Switzerland (n = 4), Germany (n = 2), Brazil (n = 2), China (n = 1), Romania (n = 1), Lebanon (n = 1), Canada (n = 1), Spain (n = 1), Mexico (n = 1), France (n = 1), Australia (n = 1), India (n = 1) and two throughout the USA and Canada.

The sample sizes taken into consideration were variable from 27 [47] to 7.306 [62] patients (more details are reported in Table III). Characteristics of the population were not specified in all studies. In the ones that mentioned information on target population, the mean age of the sample was from 28 [43, 63] years to 57 years [66], and male gender was the one most represented [42, 46-49, 52, 53, 55, 57, 59, 60, 61, 63-65, 67].

The most frequent underlying diseases requiring IC were neurogenic bladder dysfunctions secondary to Spinal Cord Injuries (SCI) [45, 38, 40, 44-46, 48-50, 52-55, 57, 59-61, 63, 64, 67].

Other less reported conditions were neurogenic bladder [32, 39, 42, 58], bladder voiding dysfunction [47], spina bifida or tethered cord [51, 56], neurogenic lower urinary tract dysfunction (NLUTDS) due to degenerative disc disease, Parkinson's disease, cerebrovascular accidents, multiple sclerosis and their causes of paralysis [65,

**Tab. III.** Characteristics and main findings of the primary studies included in our review.

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Spinu A, 2012<br><br>Romania [42] | Longitudinal retrospective study | Assessment of differences regarding some specific key biological and psychometric parameters related to the use of two different types of catheters | Tot.: 45<br><br>Some patients are included in several groups:<br>• hydrophilic catheters (M: 31; F: 4; Median of age:45)<br>• hydrophilic catheters (M: 13; F: 2; Median of age: 47)<br>• third group: (M: 4; F:1; Median of age: 45) | NGB | • IC<br>• hydrophilic catheters<br>• non-hydrophilic catheters | • UTI<br>• Inflammatory episodes at scrotum level<br>• Post/intra/inter catheterization bleeding episode | The patients that used exclusively hydrophilic type of catheters (median: "None") *vs* those using exclusively non hydrophilic type of catheters (median: "One every 4 months") presented:<br>• a significantly lower number of inflammatory episodes at scrotal level<br>• a significantly lower number of post/ intra/inter catheterization bleeding episodes<br>• a very slightly lower number of UTI activations |
| Millet L, 2012<br><br>USA [43] | Randomized trial | Comparison of the rates of bacteriuria in laboring women with epidural analgesia with the use of IC *vs* continuous indwelling Foley catheterization (CIF) | Tot.:146 women<br><br>IC group: 79 patients (54.1%)<br><br>Mean Age: 28.2 ± 5.8 years | Laboring women with epidural analgesia | IC not specified | Bacteriuria | The rate of postpartum bacteriuria was significantly higher in the IC group, compared with the CIF group |
| Shen L, 2012<br><br>China [44] | Longitudinal retrospective study | Influence of different urination methods (CIC *vs* non balloon catheter) on the urinary systems of patients with SCI | Tot.: 67 patients<br><br>CIC group: 15 patients | SCI | CIC | UTIs | UTIs:<br>• 0 event: 3 patients (33.3%)<br>• 1 event: 7 patients (46.7%)<br>• 2 events: 2 patients (13.3%)<br>• > 3 events:1 patient (6.7%)<br>Renal function impairment: 1 patient (6.7%) |

Tab. III. *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Krebs J, 2013<br><br>Switzerland [45] | Prospective cross-sectional study | Investigation of residual urine volumes after IC and the effect of residual urine on the rate of symptomatic UTIs | Tot.: 60 men<br>Median age: 47.9 years | SCI | IC<br>• Two individuals used non-hydrophilic-coated catheters with a lubrication gel | UTIs | There was no significant difference between the residual urine volume of men with recurrent UTIs and the volume of those with sporadic UTIs<br><br>Annual rate of UTIs:<br>• Men with sporadic UTIs: 0.0 (0.0/1.0)<br>• Men with recurrent UTIs: 5.0 (3.8/7.0)<br><br>The small residual urine volumes generally observed after IC do not predispose for UTIs |
| Böthig R, 2013<br><br>Germany [46] | Longitudinal Prospective study | Assessment of the incidence of UTI after urodynamic examination in patients with SCI according to bladder management | Tot.: 133 patients<br><br>M: 116 patients<br>Age interval: 19-79 years (mean 45)<br><br>F:17 patients<br>Age interval: 32-75 years (mean 60) | SCI | IC<br><br>• ISC: 51 patients<br><br>• IC by attendant (trained nurse): 63 patients | • UTIs<br>• Bacteriuria | • 40 out of 51 ISC patients (78.43%) did not show signs of either significant bacteriuria (SBU) or UTI post urodynamic studies. In 4 patients (7.84%) a SBU was ascertained while the remaining 7 (13.72%) developed UTI<br><br>• 48 out of 63 patients (76.2%) with IC by attendant remained without SBU or UTI, 5 patients (7.93%) developed SBU and 10 patients (15.87%) UTI |
| Batista-Miranda JE, 2014<br>Spain [47] | Longitudinal retrospective study | Evaluation of usefulness and morbidity of CIC | Tot.: 27 patients<br><br>F: 15 (56%)<br>M: 12 (44%) Mean age: 54.33 years (32-82) | BVD | CIC | • UTIs (cystitis and orchitis)<br><br>• Urethral strictures | UTIs were registered in 9 patients (33%, 2 women and 7 men), as mild cystitis in 7 patients and orchitis in 2 patients. |
| Bartel P, 2014<br><br>Switzerland [48] | Longitudinal Retrospective study | Assessment of the occurrence of bladder stones in patients with SCI | Tot.: 2825 patients<br>Patients with bladder stones: 93 (3.3%)<br>M: 69(74.2%)<br>F: 24(25.8%) | SCI | IC not specified | Bladder stones | • Bladder stones: 2%<br><br>Long interval to stone development: 116 (2-480) months<br>Short time to recurrence: 26 (4-79) months |

Tab. III. *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Lopes MA, 2014<br>Brazil<br>[49] | Cross-sectional study | Investigation of factors affecting the adequate continuous use of IC | Tot.: 49 patients<br>M: 40 (81.6%)<br>F: 9 (18.4%)<br>Average age: 33.9 years | SCI | CIC<br>• self-catheterization: 32 (65.3%)<br>• assisted CIC: 13 (26.5%) | • Vesicolithiasis<br>• Hydronephrosis or ureteral dilation<br>• Urinary infection<br>• Urethral trauma<br>• Urinary leakage during the intervals | Vesicolithiasis: 28.2%<br>Hydronephrosis or ureteral dilation: 18.4%<br>Urinary infection: 20.0% (diagnosed before the beginning of the study)<br>Urethral trauma: 12.2%<br>Urinary leakage: 33.0% |
| Krebs J, 2015<br>Switzerland<br>[50] | Longitudinal retrospective study | Occurrence, characteristics and clinical consequences of urethral strictures in men with NLUTD | Tot.: 1418 patients<br>IC group: 415 patients<br>M:100%<br>Mean age: 41 years (range 19-74 years) | NLUTD<br>• traumatic SCI: (92.4%) | IC | • UTIs<br>• Urethral strictures | A total of 427 UTIs' events were observed in patients using IC. The occurrence rate of urethral strictures (25%) was significantly higher in men using IC than in men using other bladder evacuation methods (14%) |
| Chaudhry R, 2017<br>USA<br>[51] | Longitudinale retrospective study | Identification of risk factors for recurrent UTI in individuals managed by CIC | Tot.: 194 patients | Spina bifida or tethered cord | CIC | UTIs | In a cohort of 194 neurogenic bladder patients utilizing CIC, 48 (25%) had frequent symptomatic UTIs<br>• Infrequent (≤ 1.0 UTI/study year) UTI in adults > 18 years group: 75 (82%)<br>• Frequent (> 1.0 UTI/study year) UTI in adults > 18 years group: 16 (18%) |
| Gao YL, 2017<br>USA<br>[52] | Longitudinal retrospective study | Types and management of urologic complications in SCI and identification of their risk factors | Tot.: 43 patients<br>M: 28 (65%)<br>F: 15 (35%)<br>Median follow-up (y, post injury): 45 (40-50) | SCI | CIC | • Bladder stone<br>• Autonomic dysreflexia<br>• Hydronephrosis<br>• Autonomic dysreflexia<br>• Urethral injury | • Bladder stone: 10%<br>• Hydronephrosis: 5%<br>• Autonomic dysreflexia: 8%<br>• Urethral injury: 22% |

**Tab. III.** *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Cornejo-Davila V, 2017<br><br>Mexico<br>[53] | Longitudinal retrospective study | Report of the incidence of urethral stricture and its management in patients with SCI treated with CIC | Tot.: 675 patients<br><br>CIC group: 333 patients<br><br>M: 250<br>F: 83<br>Mean age at the time of injury: 27 years (standard deviation ± 12.3) | SCI and NGB | CIC | • Bladder stones<br>• Urethral stricture | The most common complication of CIC was development of bladder stones (10%)<br><br>All patients with urethral stricture (4.2%) were men. Twelve patients had the stricture in the bulbar urethra, one patient had a meatal stricture and other patient had it in the penile urethra |
| Lane GI, 2018<br><br>USA<br>[54] | Cross-sectional study | Description of motivations behind transitions between IC and indwelling catheters | Tot.: 100 patients<br><br>IC group: 53 patients<br>M: 50 (93%)<br>Median age at time of survey:63 (54,70) | tSCI | IC | • Hematuria<br>• Pain<br>• UTI<br>• Lower urinary tract symptoms | Reasons for discontinuing IC included inconvenience (n = 5), physician recommendation (n = 5), patient dislike (n = 4), other-not specified (n = 3), UTI (n = 3), urinary incontinence between catheterization (n = 3), poor dexterity (n = 2), unsure (n = 2), dependence on others (n = 1), and renal failure (n = 1) |
| Myers JB, 2019<br><br>USA and Canada<br>[55] | Longitudinal prospective study | Differences in bladder related symptoms and quality of life for 4 common bladder management methods | Tot: 1479 patients<br><br>M: 60%<br>F: 40%<br>Median age: 44.9 years<br><br>Performing CIC group: 754 patients<br><br>• 62% paraplegic<br>• 31% tetraplegia | SCI:<br>• Paraplegia<br>• Tetraplegia | CIC | Bladder symptoms:<br>• Incontinence<br>• Storage and voiding, and its consequences (chronic pain, injury completeness and hospitalization for UTIs) | Results of NBSS incontinence:<br><br>• 12.2% (paraplegia)<br>• 86%(tetraplegia)<br><br>Results of NBSS storage + voiding:<br><br>• 7.8% (paraplegia)<br>• 8% (tetraplegia) |
| El Akri, 2019<br><br>France<br>[56] | Longitudinal retrospective analysis | Assessment of the relative risks of pelvic organ prolapse (POP) and urinary complications in adult spina bifida patients with neurogenic acontractile detrusor voiding with Valsalva vs those using CIC | Tot: 55 patients<br><br>• IC group: 27 patients<br>F: 18 (66.7%)<br>M: 9 (33.3%) | Spina bifida | CIC | • Risks of POP<br>• Urinary complications (UTIs or renal problems) | • Rate of POP de novo: 3.7%<br>• Vaginal prolapse: 11.1% (women)<br>• Upper urinary tract stones (urinary complications): 3.7% |

Tab. III. *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Crescenze IM, 2019<br><br>USA<br>[57] | Longitudinal Prospective study | Identification of factors associated with low urinary quality of life (QoL) in adults performing CIC | Tot.:1479 adults<br>• CIC group: 753<br><br>F: 32.9% (248/753)<br>M: 67.1% (505/753)<br>Median age: 43.2 (18-86) years | SCI | CIC | • UTIs<br>• Hospitalization<br>• Pain<br>• Severe bowel dysfunction | • ≥ 4 UTIs per year: 27.8% (209/753)<br><br>• UTI-related hospitalization within 12 months: 10.4% (78/753)<br><br>• Chronic pain: 66.3% (498/751)<br><br>• Severe bowel dysfunction: 35.9% (270/753) |
| Calisto FCFS, 2019<br><br>Brazil<br>[58] | Prospective randomized Trial | Evaluation of the performance of a new device compared with CIC | Tot: 177 patients<br>CIC group: 87 patients<br>Age:<br>• 18-30 y: 18 (20%)<br>• 31-43 y: 21 (19%)<br>• 44-58 y: 8 (10%) | NGB | CIC | UTIs episodes | The number of UTI episodes was compared between experimental group and CIC group at 6 months, with a significant statistical difference between groups. Experimental group presented a significant reduction (rate of reduction of two episodes) in the number of episodes after the use of the device. Infection reduction was also found in CIC, but less significant than in the other group. |
| Roth JD, 2019<br><br>USA<br>[59] | Retrospective cross-sectional study | Assessment of UTIs frequency and severity | Tot.:1479 patients<br><br>CIC group: 753 patients<br><br>M: 504 (66.9%)<br>F: 248 (32.9%)<br>Age mean (SD): 43.7 (13.1) | Acquired SCI | CIC | • UTIs<br>• UTIs hospitalization | UTI frequency was classified as 0, 1-3, 4-6, or > 6 over the prior year.<br><br>UTI rate based on CIC bladder management in the last year [N (%)]:<br><br>• 0: 172 (22.8%)<br>• 1-3: 372 (49.4%)<br>• 4-6: 117 (15.5%)<br>• > 6: 92 (12.2%)<br><br>UTI hospitalization in the last year [N (%)]:<br><br>• Yes: 82 (10.9%) - No: 671 (89.1%)<br><br>The adjusted odds of increased UTI frequency (reference: Void) were 3.42 (2.25-5.18, p < 0.001) for CIC |

Tab. III. *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Hennessey DB, 2019<br><br>Australia [60] | Longitudinal prospective study | Determination of the rate of UTI in patients with a new SCI and bladder management technique associated with the lowest rate of UTI | Tot.: 143 patients<br><br>M: 107 (75%)<br>F: 36 (25%)<br>Median age: 42 (27-61) years<br><br>Intermittent self-catheterization (ISC) group: 74 (51%) patients | SCI | ISC | UTIs | UTI occurred in 26.6% with ISC. The UTI rate for patients performing ISC were 6.8 UTI/1000 inpatient days |
| Anderson CE, 2019<br><br>Switzerland [61] | Longitudinal prospective study | Understanding the occurrence of and risk factors for UTIs | Tot.: 369 patients<br><br>F: 121 (32.8%)<br>M: 248 (67.2%) | SCI | • Assisted IC<br>• Self-IC | UTIs | Catheter users consistently had higher adjusted IRs for UTI than spontaneous voiders<br><br>• Patients with exactly 1 UTI: 97 (26.3%)<br>• Patients with 2 or more UTIs: 62 (16.8%)<br><br>The incidence rate (IR) ratios of UTIs were:<br><br>• assisted IC: 6.05 (95% CI 2.63-13.94);<br><br>• self-IC: 5.16 (95% CI 2.31-11.52) |
| | | | | | | | |
| Garbarino LJ, 2020<br><br>USA [62] | Longitudinal prospective study | Assessment of the risk of postoperative UTIs compared with indwelling catheterization | Tot: 7306 patients<br><br>• 285 (3.9%) patients who had IC only<br><br>• 327 (4.5%) patients who had both indwelling and IC | Total hip arthroplasty (THA) patients | IC | • UTIs due to postoperative urinary retention (POUR) | Patients requiring IC (12.6%) and both indwelling and IC (22.6%) were found to have an increased risk compared to patients not requiring catheterization, who had a 4.9% rate of UTI |

Tab. III. *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Neyaz O, 2020<br><br>India<br>[63] | Longitudinal prospective study | Understanding of changes in cystometric parameters in individuals practicing clean intermittent self-catheterization and incidence of UTI | Tot: 31 patients<br><br>M: 29 (93%)<br>F: 2 (7%)<br>Mean age: 28.6 ± 9.2 years | SCI | ISC | UTIs | A total of 60 episodes of UTI were reported. Most of these, 42 episodes (70%), were seen in patients with overactive detrusor. Mean UTI incidence = number of UTI incidents/ duration of observation (months) = 60/313 = 0.191 episodes/ patient/month which is 0.636 episodes/100 patient/day or 2.29 episodes/ patient/year. |
| Patel DP, 2020<br><br>USA e Canada<br>[64] | Longitudinal prospective study | Understanding reasons of CIC cessation | Tot: 1479 patients<br><br>• CIC group: 176 patients<br><br>F: 66 (37%)<br>M: 110 (63%)<br>Mean age: 45.3 years | SCI | CIC | • UTIs<br>• Urinary leakage | Among the entire cohort, convenience (36%), urinary leakage (20%), and the number of urinary infections (19%) were the most common reasons for CIC cessation |
| Moussa M, 2021<br><br>Lebanon<br>[65] | Prospective trial | Assessment of whether daily bladder instillation of povidone-iodine (PI) solution can help to reduce recurrent UTIs, ED visits, and hospitalization for patients with lower urinary tract dysfunction on CIC | Tot.: 119 patients<br><br>M: 91 (76.5%)<br>F: 28 (23.5%)<br><br>Mean age: 36 years | Neurogenic lower urinary tract dysfunction (NLUTD)<br><br>SCI (62.1%)<br><br>Spina bifida (8.4%)<br><br>MS (7.6%)<br><br>Cerebro vascular accident (7.6%)<br><br>Parkinson's disease (7.6%)<br><br>Degenerative disc disease (6.7%) | CIC | • Symptomatic UTIs<br>• ED visits for UTI<br>• Inpatient hospitalizations for UTI | Pre PI bladder irrigation<br><br>1. Symptomatic UTIs/year<br>• 4 episodes: 33.6%<br>• 5 episodes: 47.1%<br>• > 5 episodes: 19.3%<br><br>2. ED visits for UTI<br>• 3 visits:4.2%<br>• 4 visits: 29.4%<br>• > 4 visits: 66.4%<br><br>3. Inpatient hospitalizations for UTI, n (%)<br>• 1 hospitalization: 1.7%<br>• 2 hospitalizations: 7.6%<br>• 3 hospitalizations: 34.5%<br>• > 3 hospitalizations: 56.3% |

**Tab. III.** *follows.*

| Author, Year and Country [Ref.] | Study type | Objective | Sample size/ population characteristics | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|---|
| Angermund A, 2021<br><br>Germany [66] | Longitudinal retrospective study | Evaluation of the standard of care and the burden of illness in German individuals who perform IC and obtain recommendations for improvement of care | Tot. 1100 patients<br><br>F: 54%<br>M: 46%<br>Median age: 57.3 years | Urologic diseases (47%)<br><br>SCI (16%)<br><br>Other injuries affecting the spinal cord (12%)<br><br>MS (10%)<br><br>Other causes of paralysis (6%)<br><br>Stroke (4%)<br><br>Spina Bifida (4%)<br><br>Parkinson's disease (3%) | IC | • UTIs (and its complication)<br>• Urethral bleeding<br>• Urinary stricture | UTIs were shown to increase the number of hospital admissions and length of stay. 13% of the German population (compared to 50% of IC users in this study) have at least one hospital stay per year and stay for on average of 7.3 days (compared to 10 days of IC users in the study). |
| Walter M, 2021<br><br>Canada [67] | Cross-sectional study | Prevalence of complications associated with IC | Tot.: 130 SCI wheelchair athletes<br><br>F:18 (14%)<br>M:112 (86%)<br><br>Participants performing IC: 84% (109/130) | SCI | IC<br><br>Non-hydrophilic catheters: 62%<br><br>Single-use of catheters: 59%<br><br>Lubrication:61%<br><br>Frequency of 6-7 catheterizations/ days: 45%<br><br>Size 14 Fr catheters: 57%<br><br>Straight tipped catheters: 70% | • UTIs<br>• Urethral injury<br>• Pain<br>• Blood<br>• Inflammation/ infection of genital organs<br>• Drugs for UTIs | Overall, 84 athletes (77%) reported to have experienced at least one complication associated with IC since sustaining their SCI<br><br>• One episode of UTI during the last 12 months: 63% (69/ 109)<br>• At least one course of antibiotic treatment for UTI during the last 12 months: 52% (57/109)<br>• Urethral injury: 27% (29/109)<br>• Pain during IC: 28% (30/109).<br>• Blood on the catheter after IC: 43% (47/109)<br><br>In the subgroup of male athletes (95/109), 23% of participants (22/95) reported at least one episode of inflammation/ infection of genital organs. |

BVD: Bladder Voiding Dysfunction; CIC: Clean Intermittent Catheterization; IC: Intermittent Catheterization; ISC: Intermittent Self-Catheterization; UTIs: Urinary Tract Infections; ISC: Intermittent Self-Catheterization; CIF: Indwelling Foley Catheterization; NBG: Neurogenic Bladder; NBSS: Neurogenic Bladder Symptom Score; NLUTD: Neurogenic Lower Urinary Tract Dysfunction; SCI: Spinal Cord Injury; tSCI: Traumatic Spinal Cord Injury.

**Tab. IV.** Characteristics and main findings of the review included in our study.

| Author, year [Ref.] | Study type | N. of studies included | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|
| Wyndaele JJ, 2012 [32] | Literature review | - | Neurological or non-neurological bladder dysfunctions | CIC | UTIs | Hydrophilic catheters are superior to non-hydrophilic ones in UTI prevention. The role of the type of catheter is unclear but further exploration of special catheter types might be worthwhile. Other specific items for future research could include the role of frequency of catheterization, prophylactic antibiotics, and preservation of natural defence mechanisms in the lower urinary tract. |
| Ercole FF, 2013 [20] | Systematic review + meta-analysis | 34 articles (MA,RCT and SR) | Alterations of urinary function | IC vs different catheters | UTIs | The use of IC with clean technique results in low rates of complications or infections compared to the use of an indwelling catheter. A reduction in UTI was also obtained with a hydrophilic-coated catheter. The insertion of the catheter using the sterile technique, compared to the clean technique, suggests a relation with the reduction of UTIs. |
| Kidd EA, 2015 [33] | Systematic review | 42 trials | Hospitalized patients | IC vs indwelling or suprapubic routes for short-term catheterization | • UTIs<br>• Urethral stricture<br>• Urgency/ bladder spasms/ detrusor overactivity<br>• Asymptomatic bacteruria<br>• Pain and discomfort | Almost three times as many people developed acute urinary retention with the intermittent catheter (16% with urethral vs 45% with intermittent) |
| Biardeau X, 2016 [34] | Literature review | - | - | IC analyzed by:<br><br>Technique<br>• clean intermittent catheterization<br><br>II) Matherial<br>• single-use catheter<br>• hydrophilic-coated and pre-lubricated catheters<br>• urethral introducer | • UTIs<br>• Urethral bleeding<br>• False passage<br>• Urethral strictures | Genitourinary tract infection and urethral trauma associated with IC in neurologic patients should be managed with a global approach, including patient and caregiver education, optimal catheterization with hydrophilic-coated or pre-lubricated catheters and adequate use of antibiotic therapy.<br><br>Furthermore, the use of a urethral introducer and bacterial interference strategy could help prevent genitourinary tract infection. Among urethral complications, authors classically distinguished urethral bleeding, false passage, and urethral strictures. |
| Shamout S, 2017 [35] | Systematic review | 31 articles | SCI (adults and women with MS) | IC<br><br>• hydrophilic coated ***vs*** non-hydrophilic coated<br>• sterile technique ***vs*** non sterile technique | • UTIs<br>• Urethral trauma (bleeding, microhematuria) | Hydrophilic-coated catheters decrease the incidence of UTI as well as urethral trauma and improve patient's satisfaction when compared with non-hydrophilic-coated catheters.<br><br>Sterile technique seemed to decrease the incidence of recurrent UTI |
| Meixuan L, 2019 [36] | Systematic review + meta-analysis | 15 RCTs | Gynecologic surgery | IC ***vs*** different routes of catheterization (suprapubic drainage/ indwelling urethral catheterization) | • UTIs<br>• Hospital stay<br>• Catheter-related pain | Indwelling catheterization may increase symptomatic UTI compared with IC (RR = 2.79, 95% CI:1.09–7.14, P = 0.03). No difference was found in the rate of other complications between groups |

▶

Tab. IV. *follows.*

| Author, year [Ref.] | Study type | N. of studies included | Pathology treated with IC | Type of IC | Complications | Main findings |
|---|---|---|---|---|---|---|
| Engberg S, 2020 [37] | Scoping review | 70 articles | Neurogenic and non-neurogenic bladder problems (mainly SCI) | IC | • UTIs<br>• Urinary incontinence<br>• Urethral strictures<br>• Bladder stones<br>• Hematuria<br>• Urethral false passage<br>• Pain<br>• Squamous cell carcinoma | UTIs were more common in those using IC.<br>Higher proportion of those using IC (8%) reported urinary incontinence than those managed with an indwelling urethral catheter (1%).<br>Evidence of multiple uncommon to rare complications associated with IC were also reported, such as urethral stricture, bladder stones, changes in upper urinary tract function, and squamous cell carcinoma. |
| Chang, Shih-Chung, 2020 [38] | Systematic review | 42 articles | SCI | IC and CIC | • UTIs<br>• Epididymitis<br>• Pyelonephritis | Clean IC vs Sterile IC: no difference in UTI incidence of both groups<br><br>IC vs Without IC: UTI rate decreased after IC.<br>Self-IC had a higher reduction of UTI when compared with those used assisted IC.<br><br>CIC vs other urination methods:<br>• Epididymitis and pyelonephritis lower in CIC group<br>• UTI incidences were the same in patients with CIC and normal voiding and were lower than other urination methods<br>• UTI incidences were lower in IC groups than other urination method except in spontaneous voiding |
| Kinnear N, 2020 [39] | Systematic review | 8 articles | NGB<br>• 7 studies: SCI<br>• 1 study: neurogenic bladder from any cause | ISC | UTI | The strongest findings were in the comparison of IUC vs ISC, with IUC use associated with higher odds ratios for UTI in five of six studies (two significantly). This supports the stance of the current guidelines, which favors ISC over other catheter-based options. |
| Mitchell BG, 2021 [40] | Systematic review | 25 articles | SCI | IC | UTIs | Synthesis of these studies suggest a combined incidence of 44.2% (95%CI 40.2-48.5%) of participants having ≥ 1 UTIs per year |
| Prieto JA, 2021 [41] | Systematic review | 23 trials | - | IC with a comparison between:<br>Technique<br>• aseptic vs clean<br><br>Strategies<br>• single-use (sterile) catheter vs multiple use (clean)<br><br>III) Design of catheters<br>• hydrophilic-coated vs uncoated<br>• shorter vs standard length | UTIs | It remains unclear whether the incidence of UTI or other complications is affected by use of aseptic or clean technique, single (sterile) or multiple-use (clean) catheters, coated or uncoated catheters or different catheter lengths. |

CIC: Clean Intermittent Catheterization; Co: Comparator; IC: Intermittent Catheterization; ISC: Intermittent Self-Catheterization; IUC: Indwelling Urethral Catheterization; UTIs: Urinary Tract Infection.

66], total hip arthroplasty [62] and laboring women with epidural analgesia [36, 43].
Relating to the IC type, Clean Intermittent Catheterization (CIC) was reported in the 50% of the primary studies. The design of catheters, the information on their specific strategies and technique of bladder management were not reported in all papers. Three studies stratified the patients in those who performed self-catheterization, and those who required assisted CIC [46, 49, 61]. Moreover, Hennessey et al. 2019 [60], Neyaz et al. 2020 [63] and the review by Kinnear et al. 2020 [39] focused on complications related to intermittent self-catheterization (ISC). Instead, three studies [42, 45, 67] and three systematic reviews [35, 38, 41] compared hydrophilic and non-hydrophilic IC, or only single-use and multiple-use of IC.
All the studies revealed a variety or potential complications associated with IC. These included UTIs, urethral strictures, hematuria, bladder stones, false urethral passage, pain or discomfort, and renal dysfunctions.

*Urinary tract infections*

Urinary tract infections (UTIs) were the most reported IC complications [32]. We retrieved 16 primary studies that reported UTIs rates in patients using IC [44-47, 49-51, 54, 57-61, 63, 66, 67] and all the systematic reviews included.
Batista-Miranda *et al*. 2014 [47] pointed out that more males than females (3.5:1) undergoing CIC had a UTI. In all cases, they were mild cystitis (7 cases) and orchitis (2 patients) without evidence of pyelonephritis and/or any other severe UTI. The small residual urine volumes generally observed after IC did not predispose for UTIs as described by Krebs et al. 2013 [45]. In the retrospective study of Chaudhry et al. 2017 [51] among adult with spina bifida or tethered cord performing IC, 82% had infrequent (≤ 1.0 UTI/study year) UTIs and 16 (18%) frequent (> 1.0 UTI/study year) UTIs. Among the SCI population (n = 753) of Crescenze et al. 2019 [57], the 27.8% of patients suffered from > 4 UTIs/year with a rate of UTI-related hospitalization within 12 months of 10.4%. Roth et al. 2019 [59] classified the UTI frequency as 0, 1-3, 4-6, or > 6 over the prior years and described a rate of urinary infections in the last 1-3 years of 49.4% among 753 IC users due to acquired SCI. There were only minor differences between patients with ISC and IC by attendant (incidence of de-novo-UTIs, 8.82% and 6.67%, respectively) as reported by Bothig et al. 2013 [46] and Anderson et al. 2019 [61] (incidence rate ratios of UTIs, 5.16% and 6.05%, respectively).
In the study of Hennessey et al. 2019 [60], UTIs occurred in the 27% of patients with ISC and the UTI rate for those was 6.8 UTI/1000 inpatient days.
Neyaz *et al.* 2020 [63] described an UTI incidence of 2.29 episodes per patient per year, and more frequent in the overactive detrusor group among 31 individuals with traumatic SCI practicing self-CIC.
In the cross-sectional study of Walter et al. 2021 [67] within a group of 109 wheelchair athletes performing IC, at least one episode of UTI during the last 12 months was reported by 63% of athletes (69/109). The median number of self-reported UTI per year was one (IQR 0-2, range 0-12). More than half of the athletes (52%, 57/109) underwent at least one course of antibiotic treatment for UTI during the last 12 months. The median number of antibiotic treatments for UTI per year was one (IQR 0-2, range 0-11).
Regarding the rates of UTI following postpartum or total joint arthroplasty in patients requiring IC, an increased risk for the development of postoperative infection due to postoperative urinary retention (POUR) at both long and short-term follow-up was found [36, 62].
Angermund et al. 2021 [66] described catheter related complications among 1.100 individuals with initial IC identified in the German statutory health insurance claims data system, reporting that UTIs were the most frequent complication occurring one year before index (61%) and in follow-up (year 1: 60%; year 2: 50%).
Two primary studies compared the incidence of UTIs in IC to other bladder-emptying methods. Anderson et al. 2019 [61] evaluated 369 spinal cord-injured adults and reported no significant differences in adjusted incidence rates of UTIs among patients performing IC versus indwelling urethral catheters, while Shen et al. 2012 [44] showed that there was no significant difference in UTIs occurrence between CIC group and the normal voiding group.
Ercole et al. 2013 [20] collected studies aimed to compare CIC with clean intermittent self-catheterization and indwelling catheterization, and the clean technique with the sterile technique in relation to UTIs. From these studies, CIC resulted a safer procedure with a lower rate of complications and infections when compared to indwelling catheterization.
Conversely, Prieto et al. 2021 [41] reported unclear evidence whether the incidence of UTI or other complications was affected by use of aseptic or clean technique, single (sterile) or multiple-use (clean) catheters, coated or uncoated catheters or different catheter lengths.
In the systematic review of Kinnear et al. 2020 [39], the use of ISC was associated with lower rates of UTI than indwelling urethral catheterization (IUC) while the comparisons of IUC and suprapubic catheter vs ISC gave mixed results.
Finally, regarding prophylaxis, the use of povidone-iodine (PI) to prevent symptomatic UTIs while performing CIC was described by Moussa et al. 2021 [65], demonstrating that it was successful in decreasing the rate of UTIs, the ED visits for UTIs and the related hospitalizations. In fact, the rate of symptomatic UTIs per year was reduced by 99.2%, the rate of Emergency Department (ED) visits per year was reduced by 99.2%%, and the rate of inpatient hospitalizations for UTI per year was reduced by 99.9%. Incomplete voiding, elevated intravesical pressure, and catheter use are reported to contribute to an increased risk of symptomatic UTIs [63].

*Other IC related complications*

Repeated catheterization procedures also may result in inflammation and formation of secondary urethral stric-

tures. For example, Batista-Miranda et al. (2014) [47] investigated 27 patients using IC due to bladder voiding dysfunction and reported that 16.7% developed strictures over the mean 23.5 months of follow-up. In another study involving 333 adults with a history of spinal cord injury, 4.2% (all males) developed a urethral stricture a mean of 19.8 months after starting IC [53].

Krebs *et al*. (2015) [50] reported a higher incidence of strictures (25%) in males who used IC (n = 415) than in those using other methods to empty their bladder (14%). Such strictures were usually located at the distal part (urinary meatus, membranous urethra) or the proximal part (bulbous urethra, prostatic urethra) of the urethra, resulting from repeated urethral trauma [34].

Among urethral complications, Biardeau et al. (2016) [34] also distinguished urethral bleeding and false passage. Urethral bleeding episodes were frequent and affected as many as one-third of patients under long-term IC. False passages were also considered classical complications and often occurred in case of urethral stricture, bladder-sphincter dyssynergia and enlarged prostate [34].

Hematuria is used as an indicator to estimate urethral trauma. Patients performing exclusively hydrophilic type of catheters presented a significantly lower number of post/intra/inter catheterization bleeding episodes and inflammatory episodes at scrotal level, as reported by Spinu et al. (2012) [42].

The athletes described by Walter et al. (2021) [67] reported pain during IC (28%, 30/109) or noticed blood on the catheter after IC (43%, 47/109). In the subgroup of male wheelchair athletes (95/109), 23% of participants (22/95) reported at least one episode of inflammation/infection of genital organs.

Comparing hydrophilic-coated with standard conventional-uncoated catheters, a systematic review by Shamount S. et al (2017) [35] reported a significant decrease in the number of episodes of urethral bleeding, in the level of microhematuria or a significantly lower incidence of microhematuria with a hydrophilic catheter.

Engberg et al. (2020) [37] pointed out evidence on multiple uncommon to rare complications associated with IC, such as urethral strictures, bladder stones, changes in upper urinary tract function, and squamous cell carcinoma.

Bartel et al. (2014) [48] compared the occurrence of bladder stones in patients using different methods to empty their bladder; 2% of patients using IC had bladder stones documented on endoscopy or imaging studies. This rate was lower than patients managed with suprapubic catheters (11%) and IUC (6.6%). In contrast, the rate of bladder stones in patients managed with IC was slightly higher than that documented in males managed by reflex voiding into a condom catheter (1.1%). The time to occurrence of stones was also much longer in patients using IC (mean = 116 months) compared to suprapubic (mean = 59 months) and IUCs (mean = 31 months). The studies of Cornejo-Davila et al. [53] and Gao et al. (2017) [52] reported a rate of 10% of bladder stones, associated with urethral injuries (22%), and hydronephrosis (5%), without information on the period over which these stones occurred.

Patel et al. (2020) [64], among the entire cohort, reported convenience (36%), urinary leakage (20%), and number of urinary infections (19%) as the most common reasons for CIC cessation. Urethral trauma that occurred in six patients (12.2%) and urinary leakage during the intervals were mentioned by approximately 33% of the patients as reported in the study of Lopes et al. (2014) [49], in a small sample of 40 individuals.

In addition, Lane et al. [54] indicated that the reasons for transition away from IC were inconvenience (n = 5), UTIs (n = 3), urinary incontinence between catheterization (n = 3), poor dexterity (n = 2), unsure (n = 2), dependence on others (n = 1) and renal failure (n = 1).

Other complications were pain or discomfort associated with IC, vaginal prolapse reported in the 11,1% of the women by El Akri et al. (2019) [56]; vesicolithiasis (28.2%), followed by hydronephrosis or ureteral dilation were reported in 18.4% of a group of 49 adults with spinal cord injuries and neurogenic bladder dysfunction [49].

## Discussion

This systematic review examined evidence published between 2012 and 2021 regarding complications related to IC.

The collected evidence on common and uncommon complications is still not enough consistent and its quality varied due to heterogeneity across studies, small sample sizes and short follow-up [37].

Even though IC is considered the method of choice for bladder emptying when neurological or non-neurological causes make normal voiding impossible or incomplete, it remains a procedure that may cause many complications [32, 36]. UTIs represented the most often examined complication, with an incidence of about 44% of IC users having ≥ 1 UTIs per year [40].

The incidence of UTIs varied widely in the literature owing to differences in methodology and definitions [32].

Limited research examining sex-related differences in UTIs rates was found [43, 47]. More studies compared UTIs rates in IC with other bladder-emptying method, giving mixed results [20, 35, 38, 41, 44, 61, 62].

From these studies, comparing IC to spontaneous voiding, UTIs were most common in those using IC. On the opposite, CIC and ISC resulted safer procedures with a lower rate of complications and infections when compared to indwelling catheterization [20, 36, 39, 44, 61].

However, evidence was still unclear whether the incidence of UTIs or other complications was affected by use of aseptic or clean technique, single (sterile) or multiple-use (clean) catheters, coated or uncoated catheters or different catheter lengths [41].

The systematic review published in 2017 by Shamout et al. [35] examined different types of ICs in adults with neurogenic bladder, concluding that hydrophilic ICs tended to decrease the incidence of UTIs and hematuria and to improve patient satisfaction compared to non-hydrophilic IC.

In addition to UTIs, more common noninfectious sequelae of catheter use were described [39].
Among urethral complications, the collected studies distinguished urethral bleeding, false passage and urethral strictures [34].
Urethral strictures represented a challenge that could significantly affect bladder management with IC due to its repeated urethral trauma. False passages were also considered classical complications occurring in case of urethral stricture, bladder-sphincter dyssynergia and enlarged prostate. However, as reported by Biardeau et al. 2016 [34], the improvement of nursing care and the development of new catheters tended to decrease their incidence.
A systematic review supported the benefits of hydrophilic catheters over non-hydrophilic catheters in patients with SCI and founded that the use of hydrophilic catheters, in comparison with the standard catheter, reduced the odds of urethral bleeding and microhematuria [35]. However, the results of previous studies were contradictory. Two meta-analyses concluded that hydrophilic catheter was associated with a reduced risk of urethral bleeding compared with those non-hydrophilic, but another research suggested a higher risk of hematuria in the hydrophilic catheter group [68-70].
Other complications such bladder stones, urinary incontinence, pain, or discomfort are associated with IC. The studies of Cornejo-Davila et al. 2017 [53] and Gao et al. 2017 [52] reported a rate of 10% of bladder stones associated with urethral injuries (22%), and hydronephrosis (5%).
El Akri et al. 2019 [56] reported vaginal prolapse in the 11.1% of the women, vesicolithiasis (28.2%), followed by hydronephrosis or ureteral dilation in 18.4%.
Engberg et al. 2020 [37] also reported evidence on rare complications associated with IC, such changes in upper urinary tract function, and squamous cell carcinoma.The data collected in this review still reveal many gaps in the available evidence on the burden of IC related complications.
However, an overview of their frequency and impact could help a chief consideration in the selection of drainage methods that ensure the best treatment possible and the best outcomes for patients.
The improvement of knowledge about an optimal catheterization technique and the implementation of educational programs for patients, caregivers, nurses, and physicians are needed to improve strategy that could help the prevention of these complications [34].

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CHAPTER 2

# Research of scientific evidence: focus on urinary tract infections complications related to intermittent catheterization

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## Introduction

Urinary retention is a condition causing incomplete emptying of the urinary bladder. Te prevalence of urinary retention increases with age and is typically high in neurogenic diseases. Neurogenic urinary retention can occur in case of spinal cord injury (SCI), spina bifda (SB), multiple sclerosis (MS), or other neurodegenerative diseases. Non-neurogenic urinary retention may be caused by a physical obstruction in the urinary tract or a bladder muscle weakness [e.g., in case of cancer or benign prostate hypertrophy (BPH)] [1] or may be idiopathic. In case of urinary retention, bladder emptying can be performed by various methods, including refex voiding and catheterization. Several diferent catheterization techniques and types of catheters exist. These include indwelling catheter, suprapubic catheter, or clean intermittent catheterization [2].

Intermittent catheterization (IC) is a safe and efficacious method to treat urinary retention. However, complications can occur and the urinary tract infection (UTI) is the most important [3].

UTI is a major cause of morbidity in individuals, particularly those with neurogenic bladder. Incomplete bladder emptying leading to residual urine allows growth of leftover bacteria, which may cause permanent bacteriuria. More serious consequences of UTIs include frequent recurrences, pyelonephritis, urosepsis, renal failure, and high-level antibiotic resistance [4]. UTIs are thus among the greatest risks to people undertaking IC. Although the risk is lower than that for indwelling catheters, on average, a clean intermittent catheter user will likely experience 2.5 UTIs/year [5], with over 80% of individuals experiencing at least one UTI over a 5 year period [5].

Different types of urinary catheters, both hydrophilic-coated and non-hydrophilic (uncoated) catheters are available for IC, with an accompanying large and heterogenous body of evidence regarding their efectiveness and applicability. Recently, Barken et al. [5] issued an overview of the evidence level for a comparison of hydrophilic-coated intermittent catheters (HCIC) and non-HCIC catheters for the diferent pathologies (Tab. I).

This review found that study authors conclusions generally support HCICs over non-hydrophilic catheters for most outcomes. Hydrophilic-coated catheters have been endorsed by the majority of researchers based on strong evidence supporting improved satisfaction, preference, and QoL, and also as a means to reduce UTI frequency and adverse events. Nonetheless, some researchers, who do not observe an effect on UTI and adverse events, suggest that uncoated or even reused uncoated catheters might just as well be recommended, suggesting higher quality evidence is needed. As such, longer-term studies involving larger population sizes are needed to support the general fnding in this review that HCICs are the preferred choice in most populations [5].

Tab. I. Overview of the evidence level for a comparison of HCIC and non-HCIC catheters for the different pathologies [5].

| Population | Satisfaction | Preference | Adverse events | UTI | QoL | HEOR | Pain and discomfort |
|---|---|---|---|---|---|---|---|
| SCI | ++/– | + | ++/– – | +++/– | ++ | +++/– – | + |
| SB | +/– – | ++/– | /– – | +/– – | ++ | NA | /– |
| MS | NA | NA | NA | NA | NA | NA | NA |
| BPH | NA | NA | NA | NA | NA | NA | NA |
| Mixed | +++/– | +++ | +++/– | ++ +/– – | +++ | +++/– – | +++/– |
| All | +++/– | +++ | +++/– – | ++ +/– – | +++ | +++/– – | +++/– – |

BPH: Benign prostate hypertrophy; HCIC: Hydrophilic-coated intermittent catheters; HEOR: Health economics and outcomes research; MS: Multiple sclerosis; NA: Not available; QoL: Quality of life; SB: Spina bifida; SCI: Spinal cord injury; UTI: Urinary tract infection.
+to+++: the literature supports claims of hydrophilic catheters as being superior to uncoated catheters; – to – – – : no significant diference between hydrophilic and uncoated catheters or uncoated catheters are superior.

In order to find further evidence on the clinical-epidemiological burden of UTIs complications, which are the most common complications related to IC, we conducted a second systematic review.

## Methods

### Definition of the research question

The research question was made explicit by using the PICO model including the population under study (P), the intervention being assessed (I), comparator (C), and outcomes of interest (O). Table II describes the PICO model underlying this research.

### Search strategy

A systematic review of the literature was performed and reported according to the Preferred Reporting Items for Systematic Reviews (PRISMA) [6]. Studies were included according to stated inclusion and exclusion criteria. Four researchers carried out title/abstract screening and the selection of full texts independently. The systematic research was updated from February 2022 to March 2022 through PubMed and Web of Science with the established search strings (Tab. III).

### Inclusion/exclusion criteria

All studies focused on the clinical and epidemiological burden of UTIs related to IC and their risk factors in the adult population were considered potentially eligible. Original articles and systematic reviews published between 2012 and 2022 were selected.
Studies were excluded if they were not published in English language, did not report results for adult patients using IC or the full text article was not available.

Articles describing infections not related to the IC as well as narrative reviews, commentary, editorials, and conference presentation were excluded.
Thus, records retrieved through the search strategy were considered eligible unless they met one or more of the following exclusion criteria:

- not relevant to the condition under study;
- not English language;
- not sufficient information on any of the aspects under study;
- not full text;
- not adult population.

### Selection process and data extraction

The selection of articles followed the criteria defined in the PRISMA Statement and was independently performed by four researchers (F.D'A, F.O., C.P., A.S.). Any conflicts were resolved through discussion or involvement of a senior researcher (G.E.C.).
First, the title and the abstract were screened using the eligibility criteria. Then, the articles found to be potentially eligible were examined in full text.
Records retrieved where classified into an Excel worksheet containing for each record an ID number, the database in which it was found, indication of whether it was a duplicate or not, first author, title, journal, year of publication, a drop-down menu indicated whether it was to be included or excluded, reasons of exclusion, note and name of the reviewer who selected it.
Data were extracted from the included studies and summarized by the following results: first author's name, publication year, country, study design, characteristics of the target population, pathology treated with IC, features of IC, frequency of IC, clinical-epidemiological burden of UTIs, UTIs risk factors and main findings. When included, the systematic reviews were subjected to the snowballing process, using bibliographic references and citations in order to identify additional potentially eligible studies.

Tab. II. PICO model.

| | |
|---|---|
| Population | Adults with intermittent catheterization |
| Intervention | Intermittent catheterization |
| Comparator | - |
| Outcome | Epidemiological and clinical burden of UTIs |

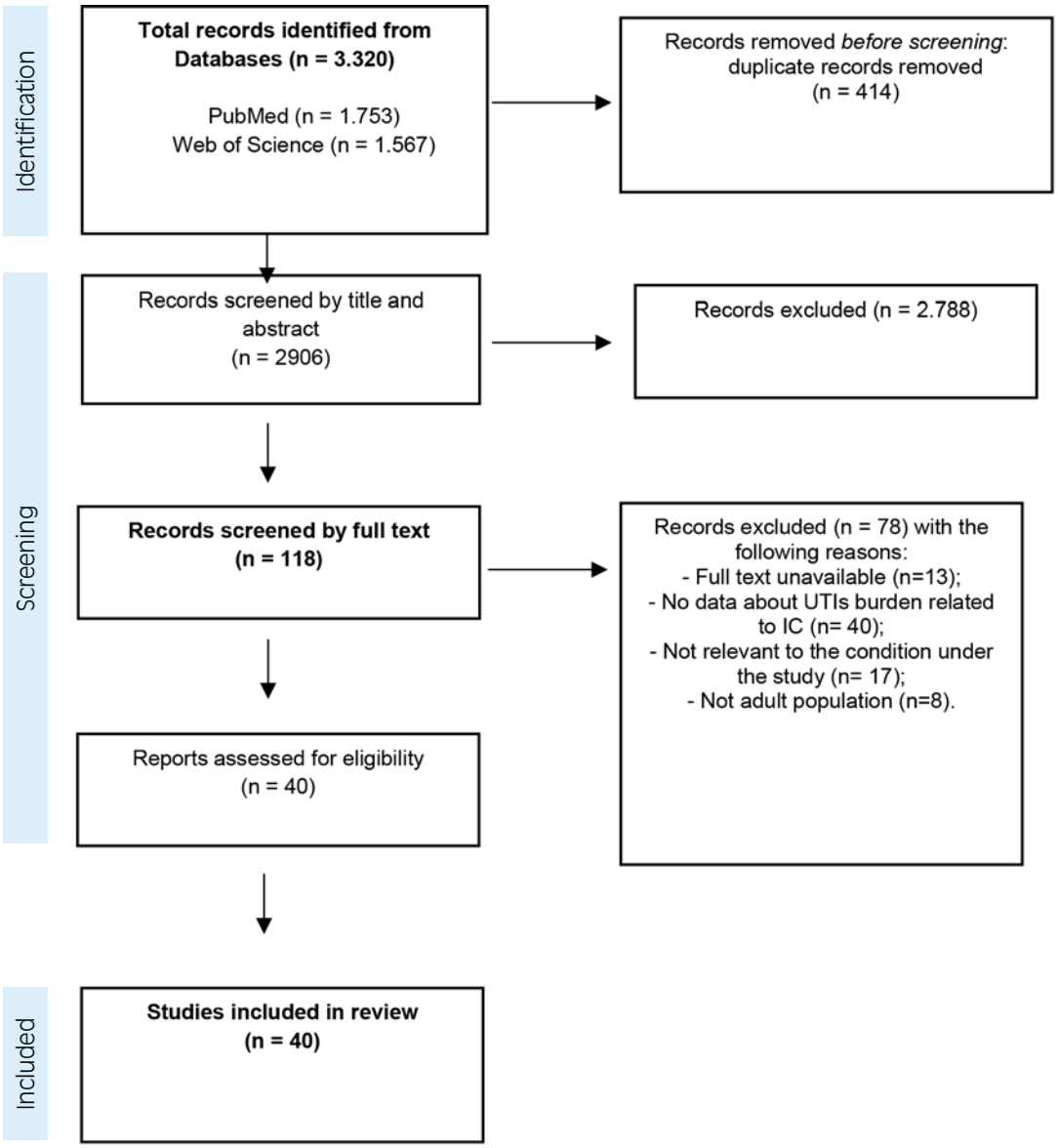
## Results

After the removal of duplicates, a total of 2.906 records was obtained from the database search. The first selec-

Tab. III. Search strings.

| Database | Search strings | Filters | N. of Articles |
|---|---|---|---|
| PubMed | ((Intermittent AND (catheterization OR catheterization)) AND (("urinary tract infection" OR "urinary tract infections" OR UTI OR UTIs))) OR (CAUTI OR CA-UTI OR "catheter-associated UTI" OR "Catheter-associated urinary tract infection" OR "Catheter-associated urinary tract infections") | Last 10 years, Humans, English, Adult: 19+ years | 1,753 |
| Web of Science | (ALL=((("intermittent catheterization" OR "intermittent catheterization") AND ("urinary tract infections" OR "urinary tract infection" OR "UTIs" OR "UTI")))) OR ALL=(("catheter-associated urinary tract infections" OR "catheter-associated urinary tract infection" OR "catheter associated urinary tract infections" OR "catheter associated urinary tract infection" OR "CAUTIs" OR "CAUTI" OR "CA-UTIs" OR "CA-UTI")) NOT ALL=("pediatric") | Last 10 years, English | 1,567 |

Fig. 1. Study selection process (PRISMA flow diagram).




tion was carried out, initially, with analysis by title and abstract and 118 full texts were chosen to read. Following the inclusion and exclusion criteria, the screening resulted in the final inclusion of 40 articles. Details about the study selection process are reported in Figure 1.

The studies, published between 2012 and 2022, used a variety of research designs and focused on different target population. We included 27 primary studies [18 longitudinal studies (45%), six cross-sectional studies (15%) and three trials (7.5%)] [7-33] (Tab. IV). We also collected 13 reviews (32.5%) (11 systematic reviews and 2 reviews) [34-46] that, to be methodologically consistent, were analyzed and presented separately in Table VI. No new studies were included after the snowballing process, because the 13 systematic reviews included studies that were already selected. Concerning the country, the 27 primary studies were conducted in the USA (8), Canada (3), Turkey (3), Germany (2), Switzerland (2), Sweden (1), Tanzania (1), Japan (1), India (1), UK (1), Lebanon (1), China (1), Australia (1) and 1 throughout the Germany and The Netherlands. The 13 systematic reviews reported international data.

The sample sizes considered varied from 22 [18] to 1.100 [33] patients. Characteristics of the population were not specified in all the studies and their details were presented in the attached Table V and Table VI.

The gender was predominantly male [8, 9, 11, 13-17, 19, 21-25, 27, 28, 30-32], and in the ones that mentioned it, the mean age of the sample was from 28.6 ± 9.2 years [30] to 72.1 years [10]. All studies provided details about the underlying diseases that made it necessary to perform the IC. The Spinal Cord Injuries (SCI) were the main cause for 19 studies [8, 9, 11-15, 17, 19, 21-28, 30, 32].

**Tab. IV.** Characteristics and main findings of the primary studies included in our review.

| 1st Author, year [Ref.] | Study type | Sample size/ population characteristics | Pathology treated with IC | Type/features of IC | Frequency of IC | UTIs (%) | UTIs risk factor | Main findings |
|---|---|---|---|---|---|---|---|---|
| Bolinger R, 2013<br>USA<br>[7] | Cross-sectional study | TOT: 44 patients<br>M: 18 (%)<br>F: 26 (59%)<br>Median age: 56.6 | NGB: 9 patients (20.5%)<br>Prostate Cancer: 2 patients (0.05%)<br>BHP: 1 patient (0.02%)<br>MS: 21 patients (47.7%)<br>SCI: 2 patients (0.05%)<br>Tetraplegia: 1 patient (0.02%)<br>Atonic bladder: 1 patient (0.02%)<br>Kidney cancer: 1 patient (0.02%)<br>Spina bifida: 1 patient (0.02%) | CIC | - | 77.2% | Personal and environmental barriers that might have increased the risk for UTIs | UTIs is the most commonly reported complication associated with CIC. Skeletal muscle spasticity acted as a barrier to CIC in patients with MS. More studies are needed to examine the occurrence of UTIs in people who reuse their catheters multiple times versus those who use single-use catheters |
| Bohtig R, 2013<br>Germany<br>[8] | Longitudinal, prospective study | TOT: 133 patients<br>M: 116 patients<br>Age interval: 19-79 years (Mean age 45)<br>F:17 patients<br>Age interval: 32-75 years (Mean age 60) | SCI | • ISC: 51 patients<br>• IC by attendant (trained nurse): 63 patients | - | Self IC group<br>UTI = 13.72%<br>UTI + SBU: 21.57%<br>De novo UTI in patients with sterile urine: 3 patients (8.82%)<br>UTI in patients with prior SBU: 4 (23.5%) patients<br>IC by attendant:<br>UTI: 15.87%<br>UTI+SBU: 23.81%<br>De novo UTI in patients with sterile urine: 6.67%<br>UTI in patients with prior SBU: 38.89% | • Elevated intravesical pressure<br>• Incomplete voiding<br>• Use of catheterization | There were only minor differences between patients with ISC and IC by attendant (incidence of de-novo-UTIs, 8.82 and 6.67%, respectively) |
| Afsar SI, 2013<br>Turkey<br>[9] | Longitudinal, retrospective study | Baseline<br>CIC group: 104 patients (63.4%)<br>F: 34 (32.7%)<br>M: 70 (67.3%)<br>After follow-up<br>CIC group: 60 patients (37.5%) | SCI | CIC<br>PVC catheters: 32 patients (53.3%)<br>Hydrophilic catheter: 28 patients (46.7%) | - | 3 UTIs frequency/ year:<br>• 93.3%<br>• once a year for hydrophilic catheter users<br>• 2 episodes per year for PVC catheter users | - | At follow-up, 44 (42%) of the 104 patients stopped using CIC. The reasons for changing the method were recurrent symptomatic UTIs, incontinence, nephrolithiasis, dependence on caregivers and urethral strictures |
| Nyman M, 2013<br>Sweden<br>[10] | Randomised control trial | TOT: 170 patients<br>IC group: 85 patients<br>M: 37 (44%)<br>F: 48 (56%)<br>Mean Age (SD): 72.1 years | Hip fracture: 57 patients (67%)<br>Osteoarthritis: 28 patients (33%) | IC | The median number of IC needed was 1 | UTIs related to IC: 8 patients (9.4%) | - | This study did not find any significant differences between IC and indwelling urinary catheterization in nosocomial UTIs |
| Yıldız N, 2014<br>Turkey<br>[11] | Cross-sectional study | TOT: 337 patients<br>IC group:<br>M: 178 (78.8%)<br>F: 65 (75.6%) | SCI | Aseptic IC | - | UTI related to IC: 51 patients (81.0%)<br>IC group without UTI: 181 patients (76.1%) | Method of urinary drainage | The frequency of symptomatic UTI was similar in the bladder management groups |
| Yilmaz B, 2014<br>Turkey<br>[12] | Cross-sectional, retrospective study | TOT CIC users: 207<br>Acute SCI group: 88 patients<br>Chronic SCI group: 119 patients | Acute and chronic SCI | CIC | - | Symptomatic UTIs: 76/207 (37%)<br>Asymptomatics bacteriuria (ASB):131/207 (63%) | - | Infection rates were higher in patients with SCI using an indwelling Foley catheter. Therefore, in order to reduce the rate of NAUTIs, the use of an indwelling catheter should be removed as soon as possible with CIC |

**Tab. IV.** *Follows.*

| 1st Author, year [Ref.] | Study type | Sample size/ population characteristics | Pathology treated with IC | Type/features of IC | Frequency of IC | UTIs (%) | UTIs risk factor | Main findings |
|---|---|---|---|---|---|---|---|---|
| Krassioukov A, 2014<br>Canada<br>[13] | Cross-sectional study | TOT: 61 paralympic wheelchair athletes<br>F: 8 (13%)<br>M: 53 (87%) | SCI | CIC | 6 ± 2 times per day (ranging from 1 to 10 per day) | Re-use 4 ± 3 UTIs per year<br>Single use: 1 ± 1 UTI per year | Re-use of catheter | The frequency of daily catheterizations was not related to the frequency of UTIs. 19 individuals (31%) reported reuse of catheters with an average of 34 ± 50 times using the same single-use catheter (ranging from 2 to 200 times per catheter). There was a significant association between frequency (number per year) of UTIs and catheter reuse: individuals who reused catheters experienced UTI more frequently |
| Rabadi MH, 2014<br>USA<br>[14] | Longitudinal, retrospective study | TOT: 161 patients<br>M: 157 (93.56%)<br>F: 4 (6.44%)<br>Median age: 59.5 ± 13.6 years (range 25-90 years)<br>IC group: 40 patients | SCI with NGB | CIC | - | UTI related to IC: 14 cases (35%) | Poor CIC technique | Patients with lumbosacral injury were able to self-void or use CIC in 76% of the cases, whereas patients with cervical and thoracic injury needed Foley or suprapubic catheterization |
| Mukai S, 2016<br>Japan<br>[15] | Longitudinal, retrospective study | TOT: 259 patients<br>M: 220 (84.9%)<br>F: 39 (15.1%)<br>Median age: 47 (12-90) | SCI associated NGB | CIC | Routinely: median value of 7 times per day | Number of febrile UTI: 67 patients (25.8%): | • Male gender;<br>• Severity of spinal cord diseases (ASIA impairment scale C or more severe) | Educating CIC patients on how best to decrease their risk of UTI is important and should be an ongoing mission.<br>Many times of CIC with keeping clean technique leading to low rate of frequency of UTI occurrence |
| Krebs J, 2016<br>Switzerland<br>[16] | Longitudinal, retrospective study | IC group: 415/1418 patients<br>M:100%<br>Mean age: 41 years (range 19-74 years) | NLUTD<br>• Traumatic SCI: 92.4% | IC | - | Approximately 70% of patients using IC suffered at least one symptomatic UTI per year<br>~ 30% of the patients using IC experienced more than two symptomatic UTIs per year | - | The bladder evacuation method, rather than patient or injury characteristic, is the main predictor for the occurrence of symptomatic UTIs in individuals with NLUTD |
| Alavinia SM, 2017<br>Canada<br>[17] | Longitudinal study | TOT: 55 patients<br>M: 42 (76.40%)<br>F: 13 (23.60%)<br>Median age: 48.31 ± 18.5 years<br>IC group: 40 patients (72.70%) | Subacute SCI | CIC<br>• Self catheterization<br>• Non self (nurse) catheterization | - | UTI related to IC: 26 (81.30%) cases<br>Bladder management method:<br>• 72.70% of UTI was in those on CIC<br>• 46% of UTI cases had nurses performing CIC | • Learning time of IC technique by patients<br>• Nursing care (i.e., hand washing, aseptic techniques, etc.) | The time when individuals with SCI were learning CIC and were being assisted by nurses was associated with a higher likelihood of UTI.<br>It is essential that nurses have the necessary expertise to provide optimal care and minimize the problems associated with routine CIC |
| Cox L, 2017<br>USA<br>[18] | Longitudinal, prospective study | TOT: 22 patients | NB | ISC | - | Pre-intervention 4 UTIs in the preceding six-month period<br>Post-intervention Fewer symptomatic UTI's (median 4 *vs* 1 episode) and fewer courses of treatment with oral antibiotics after initiating gentamicin (median 3.5 *vs* 1) | - | Symptomatic UTIs decreased significantly from four episodes to one in a six-month period |

Tab. IV. *Follows.*

| 1st Author, year [Ref.] | Study type | Sample size/ population characteristics | Pathology treated with IC | Type/features of IC | Frequency of IC | UTIs (%) | UTIs risk factor | Main findings |
|---|---|---|---|---|---|---|---|---|
| Crescenze I, 2018<br>USA<br>[19] | Longitudinal cohort study | TOT CIC users: 753<br>F: 32.9% (248/753)<br>Median Age: 43.2 (18,0-86,0 years) | Acquired SCI | IC<br>Non self CIC (caregiver):10.9% (82/753) | CIC was used for a median of 9.5 (0-44) years since the injury | > 4 UTIs per year: 27.8%<br>UTI related hospitalization within 12 months:10.4% | - | - |
| McClurg D, 2018<br>UK<br>[20] | Three-part mixed-method study:<br>• prospective longitudinal cohort<br>• longitudinal qualitative interviews<br>• cross sectional, retrospective survey | TOT: 56 patients<br>Discontinuers CIC group: 13 patients<br>F: 11 (85%)<br>Mean Age (SD): 51.3 (10.1)<br>Continuers CIC group (at 1-year follow-up): 43 patients<br>F: 31 (72%)<br>Mean Age (SD): 49.9 (12.5) | MS | CIC | - | At baseline Discontinuers CIC group: 3 patients (23%)<br>Continuers CIC group: 22 patients (51%)<br>More UTIs at 8 months in those who discontinued CIC compared to those who continued | - | Variables relating to the nature of MS as an illness (i.e. poor balance and dexterity) and those relating to the clinical and personal support available seemed to influence a person's readiness to undertake CIC |
| Stillman MD, 2018<br>USA<br>[21] | Secondary analysis of data from a prospective clinical trial | M: 79%<br>Mean age: 41 years | SCI | IC<br>At discharge 21% were using IC<br>At 12 months follow-up, 27% were using IC | | Baseline: Prevalence of UTI: 13/35 (37%)<br>At 12 months follow-up: 12/39 (31%) | | During the first year after discharge, 3-month prevalence rates of UTI were reported.<br>Subjects with spontaneous voiding reported significantly fewer UTIs than those using IC or IDC, but there was no significant difference in UTIs between IC and IDC |
| Huang X, 2019<br>China<br>[22] | Longitudinal study | TOT: 80 patients<br>M: 49<br>F: 31<br>QCC group: 40 patients<br>M: 25<br>F: 15<br>Mean Age (SD): 56.7 ± 4.3<br>CG: 40 patients<br>M: 24<br>F: 16<br>Mean Age (SD): 57.3 ± 4.8 | SCI with NGB | CIC | - | QCC group: 4 patients (10%)<br>CG group: 13 patients (32.5%) | • Traditional nursing care of IC<br>• Varied nursing expertise of nurse team<br>• Timing of catheterization<br>• Deviation in the understanding by patients and their families<br>• Improper selection of urinary catheters<br>• Irregular hand disinfection and lack of bladder training | The active education of IC, demonstration and guidance of CIC and active communication with patients enable them to know and master disease knowledge, improving their self-management ability |
| Roth J.D., 2019<br>USA<br>[23] | Retrospective cross-sectional survey | TOT: 1479 patients<br>CIC group: 753 patients<br>M: 504 (66.9%)<br>F: 248 (32.9%)<br>Age mean (SD): 43.7 (13.1) | SCI | CIC | Mean number of daily catheterizations: 5.94 (SD 1.81) | UTI rate based on CIC bladder management in the last year [N (%)]:<br>• 0: 172 (22.8%)<br>• 1-3: 372 (49.4%)<br>• 4-6: 117 (15.5%)<br>• > 6: 92 (12.2%)<br>UTI hospitalization in the last year [N (%)]: 82 (10.9%)<br>The adjusted odds of increased UTI frequency (reference: Void): 3.42 (2.25-5.18, p < 0.001) for CIC.<br>The adjusted odds of UTI hospitalization: 2.06 (0.80-5.31) for CIC | • Younger age<br>• Female gender<br>• In-home support | - |

**Tab. IV.** *Follows.*

| 1st Author, year [Ref.] | Study type | Sample size/ population characteristics | Pathology treated with IC | Type/features of IC | Frequency of IC | UTIs (%) | UTIs risk factor | Main findings |
|---|---|---|---|---|---|---|---|---|
| Anderson CE, 2019<br>Switzerland [24] | Longitudinal, prospective cohort study | TOT: 369 patients<br>F: 121 (32.8%)<br>M: 248 (67.2%) | SCI | Assisted-IC: 41 patients (11.1%)<br>Self-IC: 32 patients (8.7%) | - | • Patients with exactly 1 UTI: 97 (26.3%)<br>F: 35 (36.1); M: 62 (63.9)<br>IC assisted: 12 patients (12.4%)<br>IC-self: 8 patients (8.2%)<br>• Patients with 2 or more UTIs: 62 (16.8%)<br>F: 8 (12.9);<br>M: 54 (87.1)<br>IC assisted: 13 patients (21.0);<br>IC-self: 6 patients (9.7) | Bladder emptying method | The incidence rate ratios of UTIs were:<br>• assisted IC: 6.05 (95% CI 2.63-13.94);<br>• self-IC: 5.16 (95% CI 2.31-11.52) |
| Henessey D, 2019<br>Australia [25] | Longitudinal, prospective study | TOT: 143 patients<br>M: 107 (75%)<br>F: 36 (25%)<br>Mean Age: 42 years (27-61)<br>ISC group: 45 patients | SCI | ISC | - | ISC: 12 patients (27%)<br>UTI rate: 6.8/1000 inpatient days | Male<br>A protracted admission<br>Delays in time to TROC<br>UTI before TROC due to bacterial colonisation | ISC and SPC are both associated with reductions in the UTI rate. However, the higher rate of UTI seen in ISC patients may be due to a combination of the learning curve, unfamiliarity with aseptic technique and a spectrum of neurological deficit, with some patients struggling to catheterize with sterility. |
| Nade ES, 2020<br>Tanzania [26] | Cross-sectional study | TOT: 48 patients<br>Performing CIC group: 23 (47.9%)<br>Inpatients: 16 (80%)<br>Outpatients: 7 (25%) | SCI | CIC<br>Individual performing CIC: 8 (16%)<br>Family members performing CIC: 15 (31.3%) | - | UTI with fever: 9 (39.2% of all patients performing CIC)<br>Inpatients: 4 (25%)<br>Outpatients: 5 (71%) | - | The obstacles to perform CIC include inability to sit (31.3%), not access to CIC equipment (58.3%), insufficient hand function (29.2%) and spasticity (14.6%). |
| Berger A, 2020<br>Germany and The Netherlands [27] | Longitudinal, retrospective chart review | TOT: 73 patients<br>F: 11 (15.1%)<br>M: 56 (76.7%)<br>Missing: 6 patients (8.2%)<br>< 60 years old: 64% | SCI | Non self IC | - | UTI at baseline: 19 patients (26%)<br>UTI during 3 months of follow up: 42 patients (57.5%), ranging from 13.7% to 45.2%<br>UTI Rate: 31,5 UTIs per 100 PMs (5.3-22.7 per 100 PMs) | Probably, history of colonization at baseline | One-half of patients developed UTI within 41 days initiating IC. |
| Patel DP, 2020<br>USA [28] | Prospective longitudinal study | TOT: 176 patients<br>M: 110 (63%)<br>F: 66 (37%)<br>Median age: 45.3 | SCI | CIC | Discontinued CIC | Number of UTIs in the last year:<br>• 0: 37 patients (21%)<br>• 1-3: 79 patients (45%)<br>• ≥ 4: 60 patients (34%)<br>Hospitalization for UTI: 29 patients (16%) | - | Convenience (36%), urinary leakage (20%), and the number of urinary infections (19%) were the most common reasons for CIC cessation. |

Tab. IV. *Follows.*

| 1st Author, year [Ref.] | Study type | Sample size/ population characteristics | Pathology treated with IC | Type/features of IC | Frequency of IC | UTIs (%) | UTIs risk factor | Main findings |
|---|---|---|---|---|---|---|---|---|
| Garbarino L, 2020<br>USA<br>[29] | Longitudinal prospective study | IC group: 285 patients (3.9%)<br>Indwelling and IC group: 327 patients (4.5%) | Hip arthroplasty | IC | - | UTI: 12.6% | - | Patients treated with urinary bladder catheterization, through any method, was significantly more likely to experience UTIs compared to patients not requiring catheterization. Patient requiring any form of catheterization were found to be at a statistically significantly higher risk for post-operative UTIs ($p < 0.001$). Indwelling catheterization was found to have an increased risk of postoperative urinary tract infections, with 17.0% of patients having this complication. Patients requiring IC (12.6%) and both indwelling and intermittent catheterization (22.6%) were found to have an increased risk |
| Neyaz O, 2020<br>India<br>[30] | Prospective longitudinal study | TOT: 31 patients<br>M: 29 (93%)<br>F: 2 (7%)<br>Median age: 28.6 ± 9.2 years | SCI | ISC | - | Mean UTI episode was 0.19 episodes/ patient/month or 2.29 episodes per patient per year | Incomplete voiding<br>Elevated intravesical pressure<br>Catheter use | UTI is more common in individuals with SCI. *E. coli* is the most common cause of UTI |
| Moussa M, 2021<br>Lebanon<br>[31] | Prospective trial | TOT: 119 patients<br>M: 91 (76.5%)<br>F: 28 (23.5%)<br>Median age: 36 | • NLUTD<br>• SCI: 62.1%<br>• Spina bifida: 8.4%<br>• MS: 7.6%<br>• Cerebro vascular accident: 7.6%<br>• Parkinson's disease: 7.6%<br>• Degenerative disc disease: 6.7% | CIC | - | Pre irrigation<br>Symptomatic UTIs/year:<br>4 episodes: 33.6%<br>5 episodes: 47.1%<br>> 5 episodes: 19.3%<br>ED visits for UTI:<br>• 3 visits: 4.2%<br>• 4 visits: 29.4%<br>• > 4 visits: 66.4%<br>Inpatient hospitalizations for UTI, n (%):<br>1 hospitalization: 1.7%<br>2 hospitalizations: 7.6%<br>3 hospitalizations: 34.5%<br>> 3 hospitalizations: 56.3%<br>Post irrigation symptomatic<br>UTIs/year:<br>• 0 episode: 53.8%<br>• 2 episodes: 32.8%<br>• 3 episodes: 0.8%<br>ED visits for UTI:<br>• 0 visit: 16.8%<br>• 1 visit: 58%<br>-2 visits: 24.4%<br>3 visits: 0.8%<br>Inpatient hospitalizations for UTI, n (%):<br>0 hospitalization: 28.8%<br>-1 hospitalizations: 62.2%<br>-2 hospitalizations: 8.4%<br>-3 hospitalizations: 0.8% | Urinary stasis<br>High bladder pressure<br>Bladder stones | Individuals performing CIC have a 4-fold-increased risk of UTI compared to those who do not perform CIC |

Tab. IV. *Follows.*

| 1st Author, year [Ref.] | Study type | Sample size/ population characteristics | Pathology treated with IC | Type/features of IC | Frequency of IC | UTIs (%) | UTIs risk factor | Main findings |
|---|---|---|---|---|---|---|---|---|
| Walter M, 2021<br>Canada [32] | Cross sectional study | TOT: 130 wheelchair athletes<br>Age: 34 (28-41, 18-55)<br>F: 18 (14%)<br>M: 112 (86%) | SCI | IC: 109/130 (84%)<br>IC (transurethral): 93 (72%)<br>IC (stoma): 3 (2%)<br>Self-catheterization<br>Catheterization through others<br>Non hydrophilic catheters: 62%, (68/109)<br>Single-use of catheters: 59%, (64/109)<br>Lubrication: 61% (67/109)<br>Size 14 Fr catheters: 57%, (62/ 109)<br>Shape of catheter tip: straight tipped catheters 70% (77/109) | Median duration of performing IC: 10 years (IQR 6-15, range 1-28).<br>Median frequency of catheterizations per day: 5 (IQR 4.5-6, range 1-10) | At least one episode of UTI during the last 12 months: 63% (69/ 109).<br>Median number of self-reported UTIs per year: 1 (IQR 0-2, range 0-12).<br>At least one course of antibiotic treatment for UTI during the last 12 months: 52% (57/109)<br>Median number of antibiotic treatments for UTI per year: 1 (IQR 0-2, range 0-11) | Probably re-use of catheter | Continued education remains a primary target to address and to attempt to reduce complications associated with IC (e.g., UTIs and urethral injuries). |
| Angermund A, 2021<br>Germany [33] | Longitudinal retrospective study | TOT: 1100 patients<br>M: 511 (46%)<br>F: 589 (54%)<br>Median age: 57.3 | • Urologic diseases: 516 patients (47%)<br>• SCI: 180 patients (16%)<br>• Other injuries affecting the spinal cord: 134 patients (12%)<br>• MS: 107 patients (10%)<br>• Other causes of paralysis: 63 patients (6%)<br>• Stroke: 40 patients (4%)<br>• Spina Bifida: 45 patients (4%)<br>• Parkinson's disease: 30 patients (3%) | IC | - | UTI 1 year before index: 669 patients (61%)<br>UTI in follow-up: year 1 60%; year 2 50%. | - | UTIs were shown to increase the number of hospital admissions and length of stay. 13% of the German population (compared to 50% of IC users in this study) have at least one hospital stay per year and stay for on average of 7.3 days (compared to 10 days of IC users in the study). Individuals who perform IC were associated with a mean of 16 GP visits per year. Approximately one third visited a psychologist per year (before and after initial IC use). |

BPH: Benign Prostatic Hyperplasia; CIC: Clean Intermittent Catheterization; CIF: Indwelling Foley Catheterization; CG: Control Group; HC: Hydrophilic Catheters; IC: Intermittent Catheterization; ISC: Intermittent Self-Catheterization; MS: Multiple Sclerosis; NGB: Neurogenic Bladder; NHC: Non-Coated Catheters; NLUTD: Neurogenic Lower Urinary Tract Dysfunction; QCC: Quality Control Circle; SCI: Spinal Cord Injury; TROC: Trial Removal of Catheter; UTI: Urinary Tract Infection.

Two studies were carried out on hip surgery patients [10, 29]. Other conditions identified were Multiple Sclerosis (MS) [20, 31], neurogenic lower urinary tract dysfunctions (NLUTD) [16, 31], neurogenic bladder [7, 18], benign prostatic hyperplasia (BPH), kidney and prostate cancers [7], degenerative disc disease, cerebrovascular accidents, and Parkinson's disease [31].

Almost all the studies specified the type of IC. Fifteen studies reported information on clean intermittent catheterization (CIC) [7, 9, 12-15, 17, 19, 20, 22, 23, 26, 28, 30, 31].

Seven studies stratified the patients in those who performed self-catheterization and those who required assisted-IC [8, 17, 19, 24, 26, 30, 32], while two studies focused only on intermittent self-catheterization (ISC) [18, 25]. On 27 primary studies, 15 reported UTIs risk factors associated with the use of IC [7, 8, 11, 13, 14, 15, 17, 22-25, 27, 30-32].

## The UTIs burden

The definition of UTI varied in the different studies, in relation to the microbiological and/or laboratory test considered and in relation to the related symptoms [27]. Several studies reported data on the percentage of UTIs in IC users, ranging between 9.4% [10] and 81.30% [17]. Neyaz et al. [30] reported an UTI average of 0.19 episodes/ patient/month or 2.29 episodes per patient per year. In the study of Berger A. et al. [27], depending on definition, 14 to 45% of 73 patients with recent SCI experienced UTIs within three months of initiating IC. The corresponding rate was 31.5 UTIs per 100 patient-months (PMs), ranging from 5.3 UTIs per 100 PMs to 22.7 per 100 PMs. About one-half of patients who developed UTIs did so within 41 days of initiating IC.

Among 753 acquired SCI patients described by Roth et al. [23], classifying the UTIs frequency as 0, 1-3, 4-6, or > 6 over the prior years, the authors found a rate of urinary infections in the last 1-3 years of 49.4%.

The frequency of UTIs three times per year was 93.3% for CIC users in the study of Afsar et al. [9], while another Swiss study reported that about 70% of male patients using IC suffered at least one symptomatic UTIs per year and 30% experienced more than two symptomatic UTIs per year [16].

In the study of Walter et al. [32], within a group of 109 wheelchair athletes performing IC, at least one episode of UTIs during the last 12 months was reported by 63% of athletes (69/109) and the median number of self-re-

**Tab. V.** Characteristics and main findings of the review included in our study.

| 1st Author, year [Ref.] | Study type | Objective | N. of studies included | Pathology treated with IC | Type/Features of IC | Main findings |
|---|---|---|---|---|---|---|
| Ercole FF, 2013 [34] | Systematic review | To seek the best evidence available in the literature concerning the knowledge produced and related to the techniques of intermittent and indwelling urinary catheterization | 34 studies | - | IC | CIC is the safest procedure and has the lowest rate of complications and of UTIs, when compared with indwelling catheterization. A lower incidence of UTI was found when sterile IC was carried out as against the clean technique. The clean technique may be used as an alternative to the sterile technique in self-IC in the home. Single use of the sterile catheter self-IC does not reduce the incidence of bacteriuria and UTI when compared to the use of a clean catheter for repeated catheterizations. Self CIC was associated with lower rates of UTI and complications of the lower urinary tract when compared to sterile indwelling catheterization. A lower incidence of UTI was found when sterile IC was carried out as against the clean technique. The hydrophilic coated catheter, when compared to the one made of plastic, reduced UTI in self-catheterization. The use of lubricating gel with PVP-I reduced the contamination of the bladder with micro-organisms during self-catheterization and in intermittent catheterization carried out by family members and caregivers in the home |
| Li L, 2013 [35] | Systematic review and meta-analysis | To identify randomized controlled trials comparing the use of hydrophilic and nonhydrophilic catheters for IC in patients with SCI, and to perform a meta-analysis evaluating the occurrence of hematuria and UTI | 5 studies | SCI | HC *vs* NHC | The use of hydrophilic catheters, in comparison with the standard catheter, reduced the odds of UTI by about 64% and reduced the odds of hematuria by about 43%. Episodes of hematuria were significantly fewer in the hydrophilic-treated group ($p < .05$) than in the noncoated catheter group. There was no significant difference in the number of patients experiencing bleeding episodes (38/55 hydrophilic; 32/59 non- hydrophilic), and no difference in the occurrence of hematuria, leukocyturia, or bacteriuria |
| Kidd EA, 2015 [36] | Review | To determine the advantages and disadvantages of alternative routes of short-term bladder catheterization in adults in terms of infection, adverse events, replacement, duration of use, participant satisfaction and cost effectiveness | 42 trials | - | IC | For indwelling versus intermittent urethral catheterization, the evidence was inconclusive for symptomatic UTIs and asymptomatic bacteriuria. No trials reported pain. The evidence was inconclusive for suprapubic versus intermittent urethral catheterization. Trials should use a standardized definition for symptomatic urinary tract infection. Further adequately powered trials comparing all catheters are required, particularly suprapubic and intermittent urethral catheterization |
| Rognoni C., 2017 [37] | Systematic review and meta-analysis | Evaluation of complication rates (UTI and urethral trauma/ haematuria) related to hydrophilic-coated catheters as compared to non-hydrophilic catheters for users who practice IC | 7 studies | Neurogenic and no neurogenic bladder (i.e. prostatic enlargement) | • IC Hydrophilic coated<br>• PVC standard catheters in | The estimate from these trials highlights a statistically significant decreased risk ratio of UTIs associated with hydrophilic catheters in comparison with non-hydrophilic ones and a risk reduction associated to hydrophilic-coated catheters was verified |

▶

Tab. V. *Follows*

| 1st Author, year [Ref.] | Study type | Objective | N. of studies included | Pathology treated with IC | Type/Features of IC | Main findings |
|---|---|---|---|---|---|---|
| Shamout S, 2017 [38] | Systematic review | Systematically review of the literature on the most appropriate material and technique to perform self-IC in the adult neurogenic population | 31 studies | SCI and women with MS | IC | Hydrophilic *vs* non-hydrophilic catheters: decrease in the number of UTI episodes with hydrophilic catheter, compared with non-hydrophilic catheters.<br>Different types of hydrophilic catheters: no significant difference.<br>Prelubricated *vs* non-prelubricated catheters: significant decrease in the incidence of UTI (7.4 *vs* 22.2%) and bacteriuria (14.8 *vs* 33.3%) with pre-lubricated catheters when compared with standard PVC catheters.<br>Catheter with introducer tip *vs* without introducer tip: a statistically significant decrease in UTI rate with the use of introducer tip catheter.<br>Sterile *vs* clean technique: a significant difference in the number of UTI episodes using a sterile catheterization technique, no difference in terms of bacteriuria |
| Meixuan Li, 2019 [39] | Systematic review and meta-analysis | To compare the effect of IC with that of CC on the incidence of postpartum UTI, urinary retention and hemorrhage in laboring women with epidural analgesia | 6 studies | Laboring women | IC | There was no significant difference between the IC and CC group, the symptomatic UTI group and the asymptomatic bacteriuria group |
| Li M, 2019 [40] | Systematic review | To assess the incidence of urinary tract infection (UTI) and complications of different urinary drainage methods (indwelling urinary catheterization, suprapubic catheterization, and intermittent catheterization) | 15 studies | Gynecologic surgery | IC | Indwelling catheterization may increase symptomatic UTI compared with intermittent catheterization. Intermittent catheterization reduced the rate of symptomatic UTI compared with indwelling catheterization. There was no difference in other aspects among the three drainage routes |
| Chang, Shih-Chung, 2020 [41] | Systematic review | Systematically review of the literature on the outcome of different intervention methods to reduce urinary tract infection incidence. | 42 articles | Adults with SCI and MS-spinal cord lesions (SCLs) | IC and CIC | Clean IC *vs* Sterile IC: no difference in UTI incidence of both groups<br><br>Self-IC had a higher reduction of UTI when compared with those used assisted IC<br><br>CIC *vs* other urination methods: UTI incidences were the same in patients with CIC and normal voiding and were lower than other urination methods<br><br>UTI incidences were lower in IC groups than other urination method except in spontaneous voiding<br><br>Hydrophilic catheters are more suitable for adults than children because of complex handling |
| Engberg S., 2020 [42] | Scoping review | To summarize evidence related to adherence to intermittent catheterization (IC), complication rates, satisfaction with IC, and its effect on health-related quality of life | 70 articles | Neurogenic and non neurogenic LUT disorders | IC *vs* different catheters<br>HC *vs* NC<br><br>Self *vs* Non self IC | UTIs are the most common complication of IC and prophylactic antibiotic therapy may reduce the risk of recurrent UTIs<br><br>Evidence also suggests that UTIs are common in adult patients using IC and there are limited and mixed research about sex-related differences in UTI rates |

Tab. V. *Follows*

| 1st Author, year [Ref.] | Study type | Objective | N. of studies included | Pathology treated with IC | Type/Features of IC | Main findings |
|---|---|---|---|---|---|---|
| Kinnear N, 2020 [43] | Systematic review | To systematically compare the impact of catheter-based bladder drainage methods on the rate of urinary tract infections (UTIs) amongst patients with neurogenic bladder | 8 studies | NGB | ISC | IC *vs* Indwelling: ISC use was associated with a lower odds ratio of UTI in five studies, although in only two were these results significant<br><br>SPC *vs* IC: The odds ratio of UTI was lower amongst patients using SPC in one study, 12 and not significantly different in the remainder |
| Ye D, 2021 [44] | Systematic review | Systematic evaluation of all available types of IC and determine which one is best suited for clinical use | 25 articles | SCI | IC | The pooled odds ratios of symptomatic UTI were lower for two ready-to-use single-use catheters (gel-lubricated non-coated catheter, OR: 0.30, 95% CI 0.095-0.86; preactivated hydrophilic-coated catheter, OR: 0.41, 95% CI 0.19-0.83) as compared to single-use non-coated catheter<br><br>GSNC were the preferred option to decrease the risk of symptomatic UTI, followed PSHC, SHC and CNC |
| Prieto AJ, 2021 [45] | Systematic review | Evaluation of different catheterization techniques, strategies and catheter designs which may affect symptomatic UTIs, other complications and user preference | 23 trials (12 RCT; 11 cross-over trials) | - | IC<br>CIC | Aseptic *vs* clean techniques: uncertain if there is any difference between techniques in the risk of symptomatic UTI<br><br>Single-use (sterile) catheter *vs* multiple-use (clean): uncertain if there is any difference between single-use and multiple-use catheters in the risk of symptomatic UTI<br><br>Hydrophilic-coated catheters *vs* uncoated catheters: uncertain if there is any difference between hydrophilic and uncoated catheters in the number of people with symptomatic UTI<br><br>One catheter length *vs* another catheter length: uncertain |
| Mitchell G, 2021 [46] | Systematic review | To identify the incidence of UTI and bacteriuria in people undertaking IC and second to determine the effectiveness of antiseptic cleaning of the meatal area prior to IC in reducing the incidence of UTI and bacteriuria | 25 studies | - | IC polyvinylchloride, Hydrophilic-coated, latex, and silicone | The proportion of participants experiencing ≥ 1 UTIs per year ranged from 15.4% to 86.6%. Synthesis of these studies suggest a combined incidence of 44.2% (95% CI 40.2-48.5%) of participants having ≥ 1 UTIs per year |

CIC: Clean intermittent Catheterization; CIF: indwelling Foley Catheterization; CNC: Clean reused Non-coated Catheter; GSNC: Gel-lubricated Single-use Non-coated Catheter; HC: Hydrophilic Catheters; IC: Intermittent Catheterization; ISC: Intermittent Self-Catheterization; LUTS: Lower Urinary Tract infections; NHC: Non-coated Catheters; NLUTD: Neurogenic Lower Urinary Tract Dysfunction; PSHC: Pre-activated Single-use Hydrophilic-coated Catheter; SCI: Spinal Cord Injuries; SHC: Single-use Hydrophilic-coated Catheter; UTIs: Urinary Tract Infections.

ported UTIs per year was 1 (IQR 0-2, range 0-12). Crescenze et al. [19] showed that patients managed with CIC who suffered from ≥ 4 UTIs/year were 27.8% of the total cohort of 753 SCI patients, with a rate of UTI-related hospitalization within 12 months of 10.4%.

As well, the recent systematic review conducted by Mitchell et al. [46], found that the most commonly reported incidence ranged between 1 and 2 UTIs per year. The proportion of participants experiencing one or more UTIs per year ranged from 15.4 to 86.6% with an incidence of 44.2% (95% CI 40.2-48.5%) of IC users having ≥ 1 UTIs per year.

Two studies were retrieved that examined the effect of some preventive prophylaxis on UTIs rates. Cox et al. [18] tested the use of gentamicin bladder instillation in patients on ISC and showed fewer symptomatic UTIs (median 4 *vs* 1 episode) and fewer courses of oral antibiotics after initiating the treatment (median 3.5 *vs* 1). The proportion of multidrug-resistant organisms in urine cultures also decreased from 58.3 to 47.1%.

In the second study, after using daily povidone iodine (PI) bladder irrigation, Moussa et al. [31] described that the rate of symptomatic UTIs was reduced by 99.2% (IRR: 0.008, 95% CI: 0.001-0.059; p < .001), the rate

of emergency department (ED) visits was reduced by 99.2%% (IRR: 0.008, 95% CI: 0.001-0.059; p < .001), and the rate of inpatient hospitalizations for UTI was reduced by 99.9% (IRR: 0.0008, 95% CI: 0.0002-0.0035; p < .001).

Angermund et al. [33], which provided real data on the use of IC in Germany, also highlighted the high burden of UTIs. Within 3 years, 1.100 individuals with initial IC were identified in the German statutory health insurance claims data system. UTIs occurred 1 year before the date of IC prescription (61%) and during the follow-up (year 1: 60%; year 2: 50%). Comparing pre- and post-index, hospitalizations and readmissions decreased by around 20%, the average length of stay decreased by 4.4 days regarding all stays and of 1.1 days regarding UTIs, suggesting that IC use may have a positive influence. A General Practitioner was visited on average 15.7 times per year, an urologist 5.2 and a psychotherapist 2.5 times per year.

### The UTIs burden comparing different types and techniques of IC

More studies compared UTIs rates in IC with other bladder-emptying methods. In the study of Stillman et al. [21] subjects with spontaneous voiding reported significantly fewer UTIs than those using IC or indwelling catheterization (IDC), but there was no significant difference in UTIs between IC and IDC.

This finding is in accord with the results of Garbarino et al. [29], which found that patients treated with urinary bladder catheterization, through any method, were significantly more likely to experience UTIs compared to patients not requiring catheterization. As well, in the study of Nyman et al. [10] there was no significant difference in the occurrence of nosocomial UTIs regardless of which method was used for urinary catheterization among a group of hip surgery patients. Of the 170 patients, 18 (11%) contracted nosocomial UTIs. The frequency of nosocomial UTIs was eight (9.4%) in the intermittent and 10 (11.8%) in the indwelling catheterization group. This difference, however, was not statistically significant.

Ylmaz et al. [12], reviewing the records of SCI patients between 2008 and 2010, found that the infection rate was significantly higher in patients using an indwelling Foley catheter (52%) than those who were using CIC (37%) and those who had catheter-free voiding function (25%) (p < 0.05).

Hennessey et al. [25] compared suprapubic vs intermittent self-catheterization, founding that they were both associated with reductions in the UTIs rate.

However, in several studies and systematic reviews, the evidence on the relationship between catheter-based bladder drainage and UTIs was inconclusive or not significant [11, 34, 36, 39, 43].

Three systematic reviews [35, 37, 38] compared hydrophilic (HC) and non-hydrophilic (NHC) IC, reporting a lower incidence and a decreased risk of UTIs in the HC group compared to the NHC group.

In a meta-analysis that examined six studies including 548 patients with SCI [35], during the implementation of CIC, the groups using HC and NHC catheters were compared and the incidence of UTIs was found to be lower in the group using hydrophilic catheters. The incidence of UTIs was two episodes per year for PVC catheter users and once a year for hydrophilic catheter users. Although the difference between the two groups was not statistically significant, the subjects who used hydrophilic catheter had less UTI than those who used PVC catheter.

Ye et al. [44] aimed to conduct a systematic evaluation of all available types of IC. In this study, the pooled odds ratios of symptomatic UTI were lower for two ready-to-use single-use catheters (gel-lubricated non-coated catheter, OR: 0.30, 95% CI 0.095-0.86; pre-activated hydrophilic-coated catheter, OR: 0.41, 95% CI 0.19-0.83) as compared to single-use non-coated catheter.

Despite a total of 23 trials collected, Prieto et al. [45] found a paucity of useable data and uncertainty of the evidence regarding substantial differences associated with the use of different catheterization techniques and strategies, and catheter designs. Likewise, the scoping review published by Engberg et al. [42] concluded that there was some evidence to suggest that HCs may be associated with lower UTI rates, but additional research was needed to support their effectiveness in preventing infections. Moreover, these studies showed no statistically significant differences in occurrence of UTIs among patients using the sterile technique versus the CIC technique [34, 38, 45].

Concerning the occurrence of UTIs in people who reuse their catheters multiple times versus those who use single-use catheters, the observational study by Krassioukov et al. [13] reported a significant association between frequency (number per year) of UTIs and catheter reuse (4 ± 3 UTIs per year *vs* 1 ± 1 UTI per year). Finally, differences between patients performing ISC and those IC assisted were investigated in two studies. Anderson et al. [24], in their prospective study among 41 assisted IC users and 32 patients performing ISC, reported incidence rate ratios for assisted-IC of 6.05 (2.63-13.94) and 5.16 (2.31-11.52) for self-IC in comparison to persons who were able to void spontaneously. Bothig et al. [8] reported only minor differences between patients with ISC and IC by attendant (incidence of de-novo-UTIs, 8.82% and 6.67%, respectively) while in the study of Hennessey et al. [25] UTI occurred in the 27% of patients with ISC and the UTI rate for those was 6.8 UTI/1000 inpatient days. Among 55 inpatients with subacute SCI, most UTIs (81%) occurred among individuals using CIC, with 46% of catheterizations performed by nurses [17].

### Factors related to complications or management transition

Among the fifteen studies that reported UTIs risk factors associated with the use of IC, an increased risk for UTIs was caused by elevated intravesical pressure, urinary stasis, bladder stones, incomplete voiding, or reuse

of catheterization [8, 13, 31, 32] as well as male gender [15, 25].
The dexterity was also reported as a common barrier to CIC, above all by those with the diagnosis of MS [7]. Instead, some authors reported a high rate of UTIs due to a combination of unfamiliarity with the technique, dependence on caregivers or poor knowledge and expertise of nurse team and families, in addition to personal and environmental barriers of each patient [7, 14, 17, 22, 23].
In the study of Nade et al. [26], CIC usage decreased to 25% in the outpatient population considered by the authors, mainly due to the unavailability and unaffordability of equipment and personnel.
Among SCI patients who had discontinued CIC, the top three self-reported reasons for CIC cessation were inconvenience, urinary leakage, and too many urine infections (≥ 4 patient-perceived UTI within the last year) [28].
In a retrospective review of SCI individuals, at discharge from rehabilitation, 104 (64%) patients were performing CIC, while the subsequent follow-up showed that only 60 (37.5%) of them continued CIC and nine (21%) had transitioned from CIC to indwelling catheter. The authors reported recurrent UTIs, urinary incontinence, urolithiasis, dependence of caregivers, and urethral strictures as reasons for discontinuation of CIC [9]. Further details are reported in Table IV.

## Discussion

This systematic review aimed to summarize the most recent literature regarding UTIs rates and their risk factors in IC users. Spinal cord injuries were the main pathologies treated with IC and reported in the studies included [8, 9, 11-15, 17, 19, 21-28, 30, 32].
However, other population groups required this kind of bladder management, like patients with multiple sclerosis or patients affected by urologic diseases [20, 31].
The epidemiological data on the UTIs burden are heterogeneous in relation to the target population studied, the size of the sample, the study design, the definition of UTIs and the basic disease considered. Several studies reported data on the percentage of UTIs in IC users, ranging between 9.4% [10] and 81.30% [17]. Furthermore, a recent systematic review indicated that the frequency of people experiencing one or more UTIs per year while undertaking IC is substantial, ranging from 15.4% to 86.6% per year [46], with an incidence of about 44% of IC users having ≥ 1 UTIs per year.
Although the reported incidence of UTIs varied considerably between studies [27], these findings showed that IC users have a significantly higher incidence of infections than the general population and highlighted the need for prevention measures [47].
The high illness burden of UTIs was also visible in elevated hospitalization rates, length of stay, readmission rates and health costs for medications [33] among IC users. It should be emphasized that also the QoL of patients could be affected by several non-health-related factors, such as pain, discomfort, time spent on catheterization, and social factors associated with catheterization [48].
However, also according to the available international recommendations, IC is considered the "gold standard" for bladder retention and recommended for individuals with lower urinary tract dysfunction or neurological conditions leading to urological conditions [33, 49].
Our results indicate that hydrophilic-coated catheters are recommended to reduce the side effects of IC in patients with bladder dysfunction. However, evidence supporting the use of this intervention and its positive significance in reducing the rate of UTI is lacking [50]. Li et al. [35] show that the use of hydrophilic catheters, compared to the standard catheter, can reduce the rate of UTIs by approximately 64%.
In a recent literature review [48], single use of catheters in adults (hydrophilic-coated or uncoated) was considered to impose a lower risk of UTI. In this regard, Krassioukov et al. [13] reported a significant association between the frequency of UTIs and catheter reuse, considering that it exposes the patient to a plethora of possible cleaning techniques and prolonged duration of catheter use. Patient adherence to cleaning method cannot be predicted and this further amplifies the risk of complications and their burden on the healthcare system.
Although IC benefits, its continuation depends on the individual's perception and symptoms improvement, clinical and family support are important variables when the patient is learning the technique [20]. In fact, in our systematic review was found that the time when individuals were learning IC and were being assisted by nurses was associated with a higher likelihood of UTIs. Therefore, high levels of knowledge and skills are required to safely manage patients requiring IC and the education of nursing staff, patients and their families is a priority recommendation to avoid or reduce complications [7, 14, 17, 22, 23].
Another reflection must be made on adherence to clean intermittent self-catheterization (CISC) procedures. Clean intermittent self-catherization is associated with favourable patient outcomes, but adherence to the procedure is not addressed in the international literature [51]. General determinants of adherence relate to knowledge, complexity of the procedure, misconceptions, fears, shame, motivation and quality and continuity of professional care. Furthermore, integrating CISC in everyday life can be difficult. In younger patients, availability of materials, physical impairments and resistance to a sickness role can further compromise adherence [51]. Issues of knowledge, fears, motivation and potential psychological impact of performing CISC should be addressed prior to deciding on CISC and instructing patients. Follow-up care should be improved to include re-evaluations of skills, discussing adherence, integrating CISC in daily activities and general coping issues [51].
Other UTIs risk factors are general conditions related to patients performing IC, inadequate frequency of emptying, poor catheterization technique and catheter care by nurse or families [7, 9, 25].

Understanding how these characteristics impact patients and the reasons that individuals decide to transition their bladder management is essential to develop shared decision-making tools and preventive strategies in order to improve the quality of life of catheter users.
Further research is needed to investigate the real burden of IC related complications, above all UTIs, which represent a real problem for many patients performing IC at long-term, and to identify the barriers to implementing IC.

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Chapter 3

# Intermittent catheterization in patients with multiple sclerosis: a narrative review

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## Introduction

### Multiple sclerosis: epidemiology and main characteristics

Multiple Sclerosis (MS) is a lifelong chronic, inflammatory condition that can affect the central nervous system (brain and spinal cord) [ICD-11, 2022]. It is the most common neurological disease in young adults. The mean age of diagnosis is approximately 30 years, with most of the patients presenting periodic neurological relapses [1, 2]. As MS usually presents at a highly productive stage of life when people are planning families and building careers, it can have a significant impact on affected individuals, their families and society. Costs are considerable and rise up with increasing level of disability [3, 4]. Compiled by the Multiple Sclerosis International Federation (MSIF), the Atlas of MS (www.atlasofms.org) is an open-source global compendium of data regarding the epidemiology of MS, and the availability of resources for people with MS reported at country, regional and global levels. The first edition was produced in 2008 in collaboration with the World Health Organization (WHO) and it was updated in 2013. A total of 2.8 million people is estimated to live with MS worldwide (35.9 per 100,000 population). MS prevalence has increased in every world region since 2013 but gaps in prevalence estimates persist. The pooled incidence rate across 75 reporting countries is 2.1 per 100,000 persons/year, and the mean age of diagnosis is 32 years. It is about twice more common in females than males [4]. As regards epidemiological data worldwide, prevalence of MS varies considerably from high levels in North America and Europe (> 100/100.000 inhabitants) to low rates in Eastern Asia and sub-Saharan Africa (2/100.000 population) [5]. In Italy, around 129,220 individuals are estimated to live with MS, with a prevalence of about 210 cases per 100,000 inhabitants, except for Sardinia, where the prevalence is higher (390 cases per 100,000) [6].

MS is characterized by five major phenotypes: the clinically isolated syndrome (CIS), relapsing–remitting (RR), primary progressive (PP), progressive-relapsing (PR), and secondary progressive MS (SP) [7, 8].

Type and severity of the disease are affected by risk factors such as genetic patterns, tobacco smoking, and exposure to air pollutants, viral infections, low vitamin D levels, and juvenile obesity as reported in Amato's et al. study [9]. A specific focus on Italy was conducted by Puthenparampil's et al. [10] defining it a high-risk country for MS, while over the last 50 years, several epidemiological studies revealed that MS incidence and prevalence in Italy mainland and Islands (Sardinia and Sicily) have progressively increased. The genetic heterogeneity of the Italian ethnicities, does not account for the dramatic increase of MS incidence and prevalence observed in Italy over the last half century that, rather, seems better explained by the effect of environmental [10].

### Multiple sclerosis: bladder dysfunction and intermittent catheterization

Almost 90% of the patients with MS experience some problems related to bladder dysfunction during their lifetime [11]. Lower urinary tract (LUT) dysfunction is common in MS and has a considerable impact on quality of life (QoL). It most often results from involvement of the spinal cord, which results in detrusor overactivity and detrusor sphincter dyssynergia. Patients with MS often describe their bladder symptoms as the "worst part" of their disease since the poor bladder control generates difficulties to the normal routine as well as heavy social and psychological burdens [11].

From the European Association Guidelines 2022, strong recommendations supplied for use of intermittent catheterization (IC), whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder. Thoroughly, instruct patients in the technique, IC risks, and provides strong recommendations in avoiding indwelling transurethral and suprapubic catheterization whenever possible [12].

IC can be performed by the patient himself and so-called intermittent self-catheterization (ISC) or by a caregiver or family member in certain cases for short or long time, thus requiring training and ability to be performed. Clean intermittent self-catheterization (CISC) is considered the method of choice for treating urinary retention connected to a neurologic base. In MS, the method seems to be widely applied in clinical practice. As long as proper application needs sufficient hand function, proper positioning, sufficient sensation, cognitive function and as

always, as well as the choice of the adequate technology and the optimal material, for patients with MS the cognitive function impairment should be evaluated and, consequently, particular attention will be given to training and follow-up. Moreover, MS being a progressive disease, the treatment could need to be changed during follow-up [13]. Shaw et al. (2008) [14] studied, through a qualitative approach, the effect of CISC on QoL of MS patients. Positive impacts were related to improvement in LUT symptoms, whereas the negative impacts resulted from the practical difficulties encountered and is also related to the psychological and cultural context of worry and stigma. The factors influencing variations in QoL impacts were sex, lifestyle, frequency, and duration of carrying out self-catheterization, technical difficulties, type of catheter, co-morbidities, and individual predispositions [14]. In Abello's et al. study (2020) it has been observed that urological complications were related to MS progression and that LUT symptoms occurred more frequently in patients who need catheterization. Generally worsening disability status in MS can predict urologic complications [15].
In the present narrative review, we aim to collect literature evidence supporting the use of IC in patients with MS, describing complications and relative risk factors, and analyzing the impact of these procedures on patients with MS.

## Methods

### Search strategy

A systematic review of the literature was carried out on 17th August 2022 and updated in October 2022 by consulting two databases (Pubmed and Web of Science) with the following keywords: "multiple sclerosis", "intermittent catheterization", "complications". Articles not published in the English language were excluded. Not further filters were applied. The search string built up is reported in Table I.

### Selection process and data extraction

All database searches were completed by a single researcher, followed by a double-blinded screening from two researchers (AS, FD'A). After removing duplicates, title/abstract screening was completed using the following exclusion criteria: type of study not relevant because written in form of books, editorials, dissertation, or case-control study; moreover, records with not pertinent topic or no full text available.
In particular, the inclusion criteria comprised studies on IC procedure, or that evaluate the causes that underly IC, risk factors for complications using IC and impact of IC on QoL in adult patients with MS.
Conflicts regarding inclusion/exclusion were resolved by a meeting between the two reviewers until all disagreements were settled. Records retrieved where classified into an Excel worksheet containing for each record first author, year of publication, title, journal, year of publication, name of the reviewer who selected it, indication whether it was to be included or excluded, and, eventually, the reasons of exclusion.
The data collected from the included records were summarized and organized in two different tables, one for the primary studies (Tab. II) and one for the systematic review (Tab. III). The main data included are, in both cases even if with few differences, the identification of the study and its objective, the characteristics of the target population and the MS subtypes (if indicated), the type of IC used and complications IC-related, the impact of IC use on QoL, and main findings.

## Results

The eight studies included with the screening process were six primary studies [16-21] and two Systematic Reviews [22, 23]. Details about the systematic review process are reported in Figure 1.
No randomized clinical trial or metanalysis were included or available after the literature research.
The variables assessed for studies have been discussed previously and focused on the characteristics of the target population, the MS subtype, the causes requiring IC, the different type of IC, the IC related complications and risk factors, the impact of IC on patient's QoL and widely the main findings or outcomes. Due to the smallness of the results found, the results will be discussed below in the form of a narrative review.
Regarding the characteristics of the target population, we found that patients with MS were predominantly female individuals with a prevalence ranging between 52.17% [21] to 82.1-85% [17, 20]. The mean age ranged from 44.92 [20] to 56.6 [18] years old.

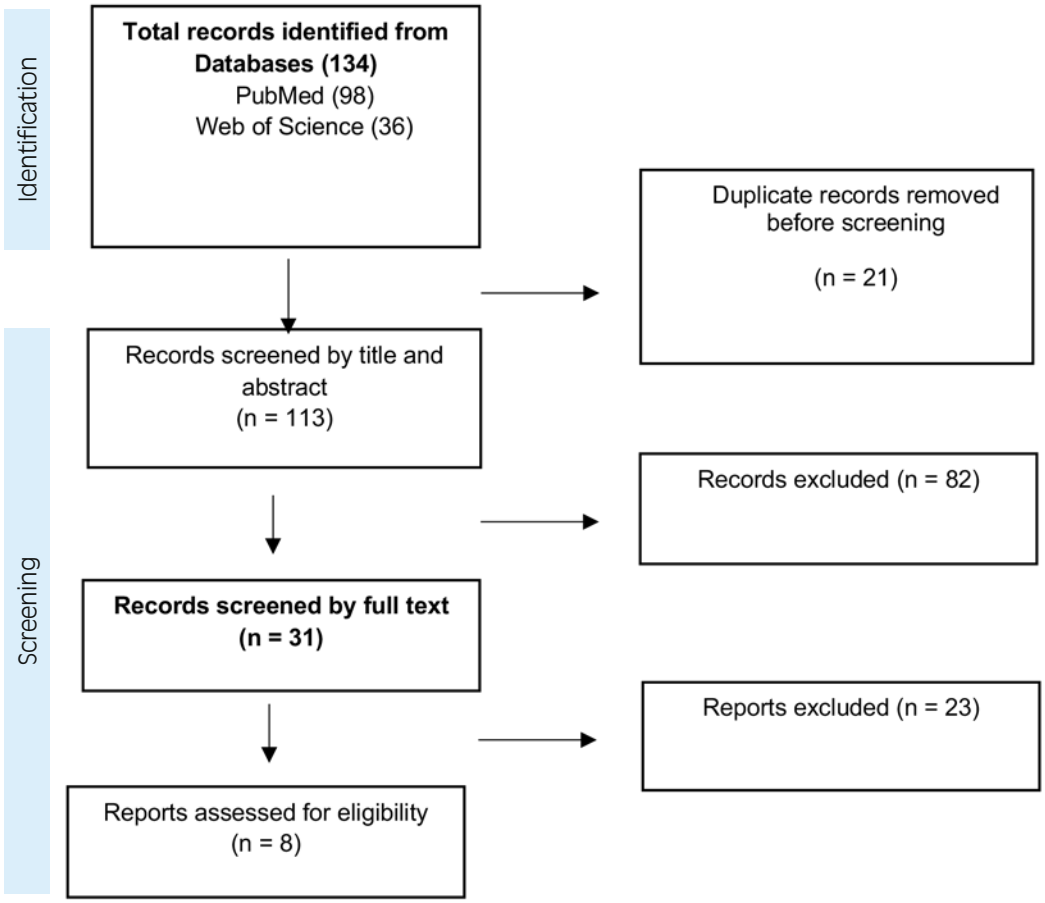
### Application of IC to patients with MS: MS subtypes and causes requiring IC

Intermittent Catheterization (IC) is a common procedure used for the management of incomplete bladder emptying in various diseases such as neurological and non-neurological causes (eg. spinal cord injury, multiple sclerosis, and benign prostatic hypertrophy). It is the act of passing a catheter into the bladder to drain urine via the urethra or other catheterisable channel. The EAU guidelines recommended clean intermittent catheterization (CIC) for patients who failed to empty their bladder [12]. CIC, in the self-administered form, (CISC) was shown to be effective in patients with MS in whom bladder involvement was up to 73-90% [24].

Tab. I. Search string and filters applied.

| Search string | Filters applied |
|---|---|
| "multiple sclerosis" AND (intermittent AND (catheterization OR catheterization)) AND complications | English language |

Fig. 1. PRISMA statement flow diagram.




Use of CIC was reported in all the studies included, making believe that CIC is the preferred option also in patients with MS. Half of the studies reported the use of clean intermittent self-catheterization (CISC) in this target population [17, 19-21].

Details about MS subtypes were reported in four studies (Tab. IV). The average range rate is 52% (39.1-56.5%), 20.5% (4.3-22%) and 26.75% (21.7-30%), respectively for RR, PP, SP, with the RR resulting the most common subtype followed by SP [16, 17, 19, 21].

In people with MS, neurogenic lower urinary tract dysfunction (NLUTD), is a common result of demyelinating damage to the central nervous system, including the brain and spinal cord, thus resulting in lower urinary tract symptoms (LUTS) that impact pwMS' QoL. Although many different treatments are available, the management of NLUTD in patients with MS remains challenging, not the least because of the progressive nature of the disease. LUTD can be managed conservatively establishing a dedicated team for a specific type of disturbance, with the aim to improve urinary continence, voiding dysfunction, and the QoL of patients, avoiding at the same time renal failure. Conservative treatments must be non-invasive or minimally invasive, so IC + pharmacotherapy (eg. antibiotics) represent the best modalities [16].

Symptoms of LUTD are common in patients with MS and prevalence increases with duration of disease and extension of spinal cord involvement. Most commonly, both storage and voiding dysfunction occur [25]. The risk factors connected to LUTD in MS disease progression are under-researched and unclear [26]. Voiding dysfunction is the consequence of detrusor-sphincter or dyssynergia (DSD) with overactivity (NDO), in the case of suprasacral spinal demyelination, or detrusor underactivity (DU), which is less common [26, 27]. In Haddad's et al. study [16], DSD occurrence detrusor overactivity (DO) was 71%, meanwhile with detrusor underactivity (DU), only 13% [16]. Instead, in Systematic Review by Cetinel et al., NDO ranged from 25 to 100% and DSD rated from 3 to 71% in the eligible studies selected [23].

The change in bladder emptying mode observed by Castel-Lacanal et al. was advised owing to urinary symptoms and related to a DSD in 16 patients, a non-relaxing urethral sphincter obstruction in 2 patients, and a detrusor underactivity (DU) in 5 patients [23].

Tab. II. Extraction data from primary studies.

| 1st Author, year [Ref.] | Study type | Aim of the study | Target population (tot, gender, median age) | MS subtype | Causes requiring IC | Type of IC | IC-related complications | Risk factors for complications | Impact of IC on QoL | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Haddad R, 2022 [16] | Single-center observational study | Determine if FIM can predict the outcome of CIC training in pwMS | Tot: 395<br>M: 117<br>F: 278 (70%)<br>Median age: 49.8 years | RR (50%)<br>PP (19%)<br>SP (30%) | DSD, with DO: (71%) or without DO (14%)<br><br>(only 13% DU) | CIC | - | EDSS (≥ 6)<br>Others probably implicated:<br>• Female genre (70%)<br>• Obesity (12% of tot. participants) | FIM is used to assess the degree of disability:<br>FIM total score: 108.0;<br>FIM motor score: 75.9;<br>FIM cognitive score: 32.1 | FIM is an independent predictor of successful CIC training in pwMS<br><br>87% of patients were successful in learning CIC |
| McClurg D, 2019 [17] | Prospective longitudinal study<br>+<br>Qualitative interviews<br>+<br>Retrospective survey | Explore the factors that affect continuation or discontinuation use of CIC | Tot: 204<br>Non-ISC: 135<br>ISC-resistant: 13<br>ISC: 56 (27%)<br><br>Started/ continued (63%):<br>43 (tot)<br>Median age: 49.9 years<br>F 31 (72%)<br><br>Started/ discontinued (36%):<br>13 (tot)<br>Median age: 51.3<br>F: 11 (85%) | Started/ continued:<br><br>RR: 21 (49%)<br>PP: 8 (19%)<br>SP: 13 (30%)<br>NK: 1 (2%)<br><br>Started/ discontinued:<br>RR: 7 (58%)<br>PP: 3 (25%)<br>SP: 2 (17%)<br>NK: 1 (2%) | MS referred to the continence service | ISC<br><br>(Single use) | UTIs<br>Started/ continued: 22 (51%)<br>Started/ discontinued: 3 (23%) | - | EQ-5D (questionnaires to measure health-related QoL self-assessment in five dimensions)<br><br>Started/ continued:<br>Mean: 62<br>General Health Status:<br>Good: 7 (58%)<br>Fair: 5 (42%)<br>Started/ discontinued:<br>Mean: 61<br>General Health Status:<br>Good: 33 (77%)<br>Fair: 10 (23%) | Although CIC may benefit many PwMS, continuation is dependent on the individual's perception of improvement in symptoms versus the burden of use. In qualitative interviews, patients reported reduced nocturia and being more comfortable and confident going out.<br><br>Retrospective survey (n = 456) was undertaken, which identified the variables that influenced CIC continuation/ discontinuation, in particular development of UTIs during learning period. |
| Bolinger R, 2013 [18] | Cross-sectional study | To examine barriers, complications, adherence, and health-related QoL in people using CIC | Tot: 44<br>M: 18 (41%)<br>F: 26 (59%)<br><br>MS: 21 (47.7%)<br><br>Median age: 56.6 years | - | NB 9 (20.5%) SCI 2 (0.05%) UTI 2 (0.05%) HPB 1 (0.02%) | CIC | • UTI: 34 (77.2%) Bleeding: 10 (22.7%)<br>• Difficulty passing the catheter: 2 (4.5%)<br>• Not comfortable doing CIC: 2 (4.5%)<br>• Stone formation: 5 (11.4%)<br>• Prostatitis: 2 (4.5%) | - | SF-36 for the assessment of health-related QoL:<br>Inadequate access to public bathrooms equipped with sinks, shelves, and adequate space<br><br>Skeletal muscle spasticity in PwMS often rendered participants dependent on others to perform CIC | This study identified both personal and environmental barriers that might have increased the risk for UTI, that is the most commonly reported complication associated with CIC. |

▶

Tab. II. *Follows.*

| 1st Author, year [Ref.] | Study type | Aim of the study | Target population (tot, gender, median age) | MS subtype | Causes requiring IC | Type of IC | IC-related complications | Risk factors for complications | Impact of IC on QoL | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Castel-Lacanal E, 2013 [19] | Single-center prospective observational study | To evaluate the impact of IC on the QoL of pwMS | Tot. 22<br>M: 8<br>F: 15 (68.18%)<br><br>Median age: 49.3 years | RR: 9 (39.1%)<br>PP: 9 (39.1%)<br>SP: 5 (21.7%) | DSD: 16<br>DU: 5<br>Non-relaxing urethral sphincter obstruction: 2 | CISC | - | - | Self-administered questionnaire (Qualiveen):<br>Before CISC – score: 1.63 ± 0.13<br>After CISC – score: 1.31 ± 0.15<br>Significant decrease in the impact of urinary disorders on the quality of life, with a decrease of the scores of three domains (bother with limitation, fears, feelings and the overall QoL score).<br>No changes in theoverall QoL assessed by the SF-36 | In patients affected by MS, IC is possible, with specialized medical and paramedical support.<br><br>IC must be proposed to pwMS, as soon as it is recommended by experts.<br><br>IC is well accepted by pwMS due to QoL improvement. |
| Fakas N, 2010 [20] | Cross-sectional study | Evaluate the rate of asymptomatic bacteriuria and symptomatic UTIs in pwMS and bladder dysfunction who practice CISC | Tot: 167<br><br>SIC group (group A):<br>Tot.: 39 (23.4%)<br>M 7(17.9%)<br>F 32 (82.1%)<br><br>Median age: 44.92 years | - | Incomplete bladder emptying | CISC | Bacteriuria (90% of group A)<br><br>Symptomatic UTIs (14% of group A) | High PVR<br><br>EDSS ≥ 6 | - | Significant proportion of pwMS who used S-IC developed asymptomatic bacteriuria.<br>It seems that prophylaxis can be effective in MS patients with bladder dysfunction and bacteriuria, independently of SIC use, if they are ambulatory and have efficient mobility (EDSS score < 6.0). |
| Vahter L, 2009 [21] | Observational study | Investigate the ability of PwMS to learn CISC | Tot: 23 pwMS<br>M: 11<br>F: 12 (52.17%)<br><br>Median age: 45.7 years | RR: 1311 (56.5%)<br>PP: 1 (4.3%)<br>SP: 6 (26.1%)<br><br>Benign: 3 (13%) | Incomplete bladder emptying and a residual volume of urine of more than 100 mL | CISC | - | - | The majority of PwMS are able to learn CISC (87%) and therefore to profoundly improve their quality of life.<br>The time needed to acquire CISC skills differed considerably depending on physical disability but not on cognitive abilities | Strong statistical evidence that an increase in disability (measured by EDSS) is associated with an increase in the number of lessons needed to acquire CISC.<br>The time needed to acquire CISC skills differed considerably depending on physical disability but not on cognitive abilities or on the course of the disease. |

FIM: Functional Independence Measure; MS: Multiple Sclerosis; pwMS: Patients with Multiple Sclerosis; IC: Intermittent Catheterization; CIC: Clean Intermittent Catheterization; SIC: Self-Intermittent Catheterization; CISC: Clean Intermittent Self Catheterization; RR: Relapsing Remitting; PP: Primary Progressive; SP: Secondary Progressive; DSD: Detrusor Sphincter Dyssynergy; DU: Detrusor Underactivity; DO: Detrusor Overactivity; C-ISC: Clean Intermittent Self Catheterization; NK: Not Known; EDSS: Expanded Disability Status Scale; LUTS: Lower Urinary Tract Symptom; NB: Neurogenic Bladder; HPB: Hypertrophy Prostatic Benign; UTI: Urinary Tract Infection; SCI: Spinal Cord Injury; QoL: Quality of Life; PVR: Post Volume Residual.

Tab. III. Systematization of evidence from systematic review.

| 1st Author, year | Study type | N. studies included | Aim of the study | Causes requiring CIC | Risk factors for complications | Impact of IC on QoL | Main findings |
|---|---|---|---|---|---|---|---|
| Tornic J, 2018 [22] | Systematic review | 3 CIC (Tot. 445 pwMS)<br>M:117 (27%)<br>F: 256 (57%)<br>GNR 72 (16%) | Assessment of all available evidence on efficacy and safety of catheterization for treating NLUTD in patients with MS | Incontinence | - | Castel-Lacanal 2013<br>QoL measured with SF-36 (overall score including: General physical score, General mental score, Physical functioning, Role physical, Bodily pain, General health, Vitality, Social functioning, Role emotional, Mental health)<br>Baseline: 1.63 ± 0.13<br>Under treatment: 1.31 ± 0.15<br>Kornhuber and Schutz 1990<br>Overall mean PVR (mL) n = 197<br>Baseline: 113<br>Under treatment: 28<br>Mean PVR (mL) in patients with PVR > 200 mL on admission n = 37<br>Baseline: 318<br>Under treatment: 83<br>Luoto 1993<br>Improvement in QoL under treatment with CIC: 89% (55/62) of pwMS – Baseline data not available (Reduction of frequency, urgency, stress and urgency incontinence, and bladder emptying has been reported) | There are beneficial effects of CIC on the urological outcome in pwMS but the evidence-base proof is very limited. |
| Cetinel B, 2013 [23] | Systematic review | 63 studies Total 5604 patients<br>(2 studies valued CIC in pwMS: Vahter 2009, Kornhuber HH 1990) | Prepare a national consensus report for the management of LUTD due to MS in light of available literature | NDO (25-100%)<br>DSD (3-71%)<br>Detrusor hypoflexia or acontractility (8-70%)<br>Detrusor hypoflexia or areflexia (3-73%)<br>Hypocompliant detrusor (7-10%) | Only one study (Giannantoni 1998) found urodynamic pathologies such as NDO, DSD, and hypo-compliant bladder as risk factors for UUT deterioration, disease progression and CIC performing capabilities | EDSS ≥ 7<br>In particular:<br>Vahter, 2009<br>87% patients with EDSS score less than 7.5 were able to perform CIC<br><br>Kornhuber HH, 1990<br>350 patients used CIC, 197 CIC was started with a PVR of 113 ml; this treatment reduced PVR mean to 28 ml, thus continence rate improved, and UTI rates reduced | This SR was not able to find any evidence-based cut off about post-void residual value for the recommendation to start CIC in MS-related LUTD. |

NLUTD: Neurogenic Lower Urinary Tract Dysfunction; MS: Multiple Sclerosis; PwMS: Patients with Multiple Sclerosis; GNR: Gender Not Reported; LUTD: Lower Urinary Tract Dysfunction; NDO: Neurogenic Detrusor Overactivity; DSD: Detrusor Sphincter Dyssynergia; UUT: Upper Urinary Tract; PVR: Post Void Residual; EDSS: Expanded Disability Status Scale.

Tab. IV. MS subtypes and relative prevalence reported in the included studies.

| MS subtypes authors | Relapsing remitting (RR) | Primary progressive (PP) | Secondary progressive (SP) |
|---|---|---|---|
| Haddad R, 2022 | 50% | 19% | 30% |
| McClurg D, 2019* | 49-59% (54%) | 19-25% (22%) | 17-30% (24%) |
| Castel-Lacanal E, 2013 | 39.1% | 39.1% | 21.7% |
| Vahter L, 2009 | 56.5% | 4.3% | 26.1% |
| **Average** | 52.00% | 20.50% | 26.75% |

* Range due to study groups: started/continued and started/discontinued relatively to IC use progression or interruption.

The two Systematic Reviews (SR) included in our review [22, 23] focused the attention on the management of NLUTS in patients with MS. Tornic et al. [22] selected and included 3 studies related to CIC [19, 28, 29]. The authors suggest beneficial effects of catheterization on the urological outcome in patients with MS, but the evidence base is very limited, arising a complete lack of RCTs reports on adverse events. Cetinel et al. [23] selected only two studies evaluating CIC in patients with MS [21, 28], without being able to find any evidence-based cut off post-void residual value for the recommendation to start clean IC in MS-related LUTD.

## IC-related complications and relative risk factors

The correct use of IC and strict compliance with hygiene instructions should avoid negative effects of continuous long-term catheterization. However, UTIs are still reported as major complication IC-related [17, 18, 20]. Other, less common IC-related complications are urethral strictures, hematuria, bladder stones, false urethral

passage, pain or discomfort, and renal scarring [31]. According to other authors, other complications IC-related, except for UTIs (77.2%), are bleeding (22.7%), difficulty passing the catheter scar tissue (4.5%), not comfortable doing CIC (4.5%), stone formation (11.4%), and prostatitis (4.5%) [18].
As reported according to the scoping review by Engberg's et al., some evidence suggests that most of the patients can successfully master IC relying on functional status, the probably most important predictor of success [31]. Accordance to that, in our narrative review, even if risk factors for IC-related complications were rarely reported, they are often related to the worsening disability, measured usually with expanded disability status scale (EDSS) [16, 20].
Among the studies found out with this review, Fakas et al. [20] observed symptomatic UTIs only in 14% of patients with MS performing self-intermittent catheterization (SIC) to solve incomplete bladder emptying. More in detail, Fakas et al. found out that a significant proportion of MS patients with bladder dysfunction under SIC developed asymptomatic bacteriuria (90%). Authors concluded that prophylaxis (nitrofurantoin or norfloxacin) could be effective in MS patients with bladder dysfunction and bacteriuria if they are outpatient and have efficient mobility (EDSS score < 6.0) [20].
In Haddad et al. [16] more than half of the participants who developed UTIs (prevalence: 51%) had also a significant mobility impairment (calculated as EDSS score > 6).

### Impact of IC utilization on MS patients' quality of life (QoL)

The primary studies selected in the present narrative review, had different aims and main findings, but all of them analyzed, from different point of views, the impact on QoL of IC in MS patients. The two systematic reviews assess the management of NLUTD, indirectly evaluating the same goal for patients (QoL).
In 1982, Goldstein reported in his study that symptomatic voiding dysfunction was present in 97% of patients with MS and sexual dysfunction was present in 71% of men sample [32]. McClurg and Bolinger found that 21% of the sample population (total baseline 20 and 44 subjects, respectively), presented dexterity issues and pain [17, 18]. The QoL is also connected to other types of barriers CIC-related, such as public bathrooms characteristics, dexterity-spasticity, positioning (female) and elements of catheter itself: size, type/material of catheter [18].
The single center prospective study by Castel-Lacanal et al. (2013) [19] evaluate QoL throughout two different questionnaires: Qualiveen® on specific urinary disorders and SF-36 to assess general health status. Author's conclusions indicate better QoL scores IC-related assuming a specialized medical and paramedical support. In fact, consequently to MS patients' acceptance of IC, the study has recorded a low dropout rate (1/23 = 4%).
In the observational study of 2009 by Vahter and colleagues [21], the ability of patients with MS to learn clean intermittent self-catheterization (CISC) was tested. The study underlines the important role of an experienced nurse in the training process. Except of this, the study recorded an ability to learn CISC technique about 87% patients with MS (tot. 23). In practical, patients with Expanded Disability Status Scale (EDSS) score < 7.5 were able to perform CIC [21].
Also, according to Haddad et al. [16], 87% patients withMS (tot. 395) were successful in learning clean-intermittent catheterization (CIC) during training sessions. The authors used the Functional Independence Measure (FIM) as an independent predictor of successful CIC training in MS patients.
McClurg's prospective longitudinal study [17] measured the general status of health in MS patients through EQ-5D (questionnaires to measure health-related QoL self-assessment in five dimensions). In the group "started/continued" (patients with MS, who didn't interrupt IC) the good feeling was recorded in 58% of the total patients. In the group "started/discontinued" (patients with MS who interrupt IC) the good health status was recorded 77% patients with MS. The same study, through a qualitative interview to MS patients practicing CIC, revealed a reduced nocturia and more comfort and confidence going out without worries about accessing to the toilets. The online survey of this study revealed that 41% of the sample continued CIC reported a QoL overall "better". Contrarily, the primary factor that favors CIC discontinuation is the development of a complications, in particular: increase in number of UTIs (51/167, 31%); poor dexterity and/or pain (35/167, 21%); felt it was humiliating/degrading (20/167, 12%); no longer necessary due to improvement (16/167, 10%) and using CIC did not improve symptoms (16/167, 10%).

## Discussion

The most of the patients with MS are female (average 70.7%) and almost 90% of MS patients experience some problems related to bladder dysfunction during their lifetime. These problems can affect their social, occupational, and sexual life. MS causes neuro-urological symptoms in 50-90% of the patients. The incidence of voiding dysfunction in MS has been reported to be 33-52% in the patients sampled consecutively, regardless of their urinary symptoms [33]. Urodynamic examinations are critical in detecting bladder dysfunction in the MS patients with urological complaints and those who do not express such complaints. This is because mild urological complaints may be overshadowed by the disturbing neurological defects such as paresis, balance problems, sensation abnormalities, spasticity, etc. Lower urinary tract disease frequently appears within the first ten years of diagnosis. Therefore, the MS patients should be evaluated with a good anamnesis and a physical examination for the urinary system and with a detailed urodynamic examination if necessary [33]. Urinary system evaluations of the MS patients in the early period, planning an appropriate treatment, and follow-up at regular intervals are critical in preventing urinary system complications.

There is a lack of comprehensive studies regarding the neurogenic bladder features of the MS patients. The urodynamic examinations revealed that detrusor overactivity (DO) was the most common finding in the MS patients, followed by detrusor sphincter dyssynergia (DSD) and detrusor hypoactivity (DO) [16, 23].
Various types of neurogenic bladder can be found in the patients with MS based on the location of white matter lesions such as suprapontine-pontine, suprasacral, sacral-infrasacral lesions. Accordingly, storage and emptying disorders occur in various proportions [34]. It was reported that the most common symptoms seen in the MS patients were (37-99%) related to storage (irritative), followed by mixed-type symptoms (34-79%) and emptying-related symptoms (obstruction) (51-59%) [25].
Urine leakage is more frequent in women than men because of the diminished urethral pressure due to the shorter urethra. Postmenopausal genital atrophy in older female patients may also play a role in this phenomenon and lead to higher rates of external collector system usage in women. Bacterial growths in urine culture (> $10^5$ CFU/mL) were significantly higher in females (35.1%). Several studies have shown that UTI is more common in women. Endogenous rectal flora has been reported to cause urinary tract infections through the fecal perineal-urethral tract [35]. The common presence of bacterial growth (> $10^5$ CFU/mL) in female urine culture is from microorganisms reaching the urinary tract via the ascending tract due to short urethra and possible stool contamination in the female patients whose diaper usage is significantly higher due to frequent leaks. Other possible explanations include the closer urethral exit to the anal region, which may facilitate stool contamination and decreased estrogen in postmenopausal women [36].
As noted by data collected from our narrative review, the rate of recommendation for IC after the urodynamic examination per MS patients was high. IC-related complications have also been studied and demonstrated to be associated mainly with UTIs. However, there is insufficient evidence to assess the relevance of relative risk factors, such as patient or injury characteristics, psychosocial or behavioral aspects, bladder evacuation method or residual urine. Several reports have documented lower UTI rates in patients using IC compared with those using transurethral indwelling catheters (TUC). However, the UTI rates for IC were increased compared with spontaneous voiding [37, 38].
Patients and injury characteristics had no significant effect on the occurrence of symptomatic UTIs, but some evidence we collected suggest most of the MS patients can successfully manage IC relying on functional status often measured with expanded disability status scale (EDSS). An EDSS ≥ 6 seems to be connected to lower IC-related complications and so positively connected to treatment continuation [16, 20].
Symptomatic UTIs have a considerable effect on QoL of individuals with NLUTD, since more serious consequences of UTIs include frequent recurrences, pyelonephritis, urosepsis, renal failure [39]. Strong evidence supports improved satisfaction, preference, and increased level of QoL with the use of CIC/CISC and these aspects meant a reduction of UTIs frequency and adverse events [17].
Being MS a worsening progressive disease, the ability to learn using the technology and the level of disability status should be evaluated over time. The majority of patients with MS can learn CISC (87%) [21], if they are supporting by expert sanitary professionals in the training period and follow-up [19].
Several limitations should be considered in our review. No Randomized control trial (RCT) or metanalysis result available on our topic of interest and articles collected from the the Systematic Reviews included in our literature research express generally low evidence. We partially solved these limitations through the research of further literature to include in the report.
In conclusion, urodynamic examinations revealed significant NLUTD in the patients MS. The consequences are urinary retention and leaking. According to all our literature research, the first method of choice to solve these problematics is CIC, mostly in the self-administered form (CISC).
The bladder evacuation method, rather than patient or injury characteristics, is the main predictor for the occurrence of symptomatic UTIs in individuals with NLUTD. In fact, contraindications to CISC use could be an increasing occurrence of UTIs, which strongly correlate with MS patients' QoL.
According to MS patients' QoL measured during IC treatment, CISC seems an appropriate urinary emptying method, assuming an opportune number of lessons and an adequate medical support. Considering that the MS findings may progress over time, all patients should be evaluated periodically for the urinary system, and the necessary modifications should be carried out in their treatments.

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Chapter 4

# Benign prostatic hyperplasia and intermittent catheterization: a literature review

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## Introduction

Over the years, intermittent catheterization (IC) has been widely recognized as a preferred technique for the management of patients with urinary retention, whether caused by neurogenic or non-neurogenic bladder dysfunction [1].
Among non-neurogenic dysfunction, one of the most common obstructive causes of urinary retention is benign prostatic hyperplasia (BPH). The purpose of this chapter was to provide an overview of the available evidence-based literature and guidelines on the use of IC in patients with BPH.
Benign prostatic hyperplasia (BPH) is an age-related, histologically identified disorder that affects men of all ages, with prevalence rates ranging from 25% in men aged 40 to 49 to more than 80% in men aged 70 to 79 [2-5]. It was estimated that worldwide more than 210 million men are affected by prostate enlargement, with 11.26 million new cases and 1.86 million Years of healthy life lost due to disability (YLD) in 2019 only [6-10].
In addition, the high illness burden was also seen in the description of BPH related costs. Approximately, £ 180 million is spent annually on BPH treatment in the UK and the estimated direct cost for BPH in the USA is around $ 1.1 billion [11].
This condition, along with post-operative urinary retention, idiopathic detrusor underactivity, and refractory bladder is classified as a non-neurogenic cause of urinary retention (UR), in opposition to the neurogenic ones (i.e. spinal cord injury, spina bifida, multiple sclerosis, or other neurodegenerative diseases) [12-14].
BPH is likely the result of a multifactorial process, including age-related changes associated with metabolic disturbances, changes in hormone balance, and chronic inflammation [15].
From a pathophysiological point of view, BPH is a histological diagnosis that refers to the proliferation of glandular epithelial tissue, smooth muscle, and connection tissue within the prostatic transition zone. This condition leads to a bladder neck obstruction and to the development of bladder outflow obstruction (BOO) through two mechanisms: prostate enlargement and constriction of the prostatic urethra from excessive alpha-adrenergic tone in the stromal portion of the gland [3-6, 16, 17].
Parallel to these anatomical and functional processes, the symptoms of BPH, also known as lower urinary tract symptoms (LUTS), increase in frequency and severity with age and are divided into those associated with storage of urine and those with voiding or emptying (Tab. I) [15].
The prevalence of LUTS attributed to BPH increases as men age. Approximately 50% of men over the age of 50 and up to 80% of men over the age of 80 experience LUTS [18].
Men may have some of these symptoms early on, but with the disease progression, the symptoms may become more prevalent, distressing, and bothersome, affecting their quality of life [19].
In fact, patients with BPH can experience great discomfort with urination and may develop important complications, including chronic (CUR) and/or acute (AUR) urinary retention, infections due to incomplete bladder emptying and renal failure [14, 19-21]. Moreover, LUTS have been shown to cause significant debility and have greater impacts on anxiety and depression than similar chronic illnesses such as diabetes, gout and hypertension [10].
Despite the more prevalent (and often first line) use of medical and minimally invasive therapy for men suffering from LUTS associated with BPH, the transurethral

Tab. I. Symptoms of benign prostatic hyperplasia (BPH).

| Symptoms of BPH |
|---|
| **Storage symptoms** |
| • Urinary frequency<br>• Urinary urgency<br>• Urinary incontinence<br>• Nocturia<br>• Dysuria |
| **Voiding symptoms** |
| • Difficulty initiating urinary stream<br>• Urinary hesitancy<br>• Straining to void<br>• Decreased urinary flow<br>• Intermittency<br>• Dribbling<br>• Incomplete bladder emptying |

Data source: Skinder D et al., 2019 [19].

resection of the prostate (TURP) is still considered the gold standard of BPH treatments [22, 23].
IC is not considered the first line of treatment in this population, although this procedure is addressed by some international guideline as a temporary treatment pre- and post-surgical intervention or recommended when long-lasting LUTS lead to serious complications as AUR or chronical conditions like CUR [23-26].
However, there is a general lack of literature and no clear consensus on IC in BPH patients and a further assessment is required to highlight current knowledge on this topic.
Therefore, the aim of this review was to summarize the existing literature concerning the use of IC in BPH patients in order to provide an overview of the current and potential impact of this device on the improvement of health and quality of life.

## Methods

### Search strategy

A systematic review of the literature was initiated in March 2022 and updated in October 2022 by consulting two databases (Pubmed and Web of Science) with the following search string:
*"((benign AND prostatic AND (hypertrophy OR hyperplasia)) AND (intermittent catheterization) AND complications)" and "((ALL=(benign AND prostatic AND (hypertrophy OR hyperplasia))) AND ALL=(intermittent AND (catheterization OR catheterization))) AND ALL=(complications)".*
To be eligible for inclusion, studies had to be published in English and report on data related to IC in patients with BPH. Articles including children and adolescent population and including only different target population other than patients with BPH were excluded as well as studies conducted in animals or in vitro. Further information was gathered from related references within the articles identified and by hand searching grey literature and scientific websites.
Synthesis of qualitative and quantitative data was undertaken using a narrative synthesis.

### Selection process and data extraction

Searching the two databases, the selection of articles followed the criteria defined in the PRISMA Statement [27] and was independently performed by two researchers (CP and FD'A). Any disagreement was resolved by discussion or by the involvement of a senior researcher (GEC).
All records were subjected to the snowballing process, using the bibliographic references and citations and additional articles that met the inclusion criteria of this review were obtained by hand searching.
Records retrieved where classified into an Excel worksheet containing for each record first author, year of publication, title, journal, year of publication, name of the reviewer who selected it, indication whether it was to be included or excluded, and, eventually, the reasons of exclusion.

## Results

A total number of 45 articles resulting from the search string were screened by title and abstract. Following the inclusion and exclusion criteria, 32 full texts were chosen to read.
Eventually, the last screening resulted in the final inclusion of six articles [26, 28-32], of which only one was included after the snowballing process [32].
Details about the systematic review process are schematized in Figure 1.
Given the lack of robust data and the numerous unresolved controversial issues on the use of IC in the management of BPH, additional evidence has been integrated and synthesized into a narrative review.
The main findings are hereafter reported, focusing on the statement of international guidelines and literature data.

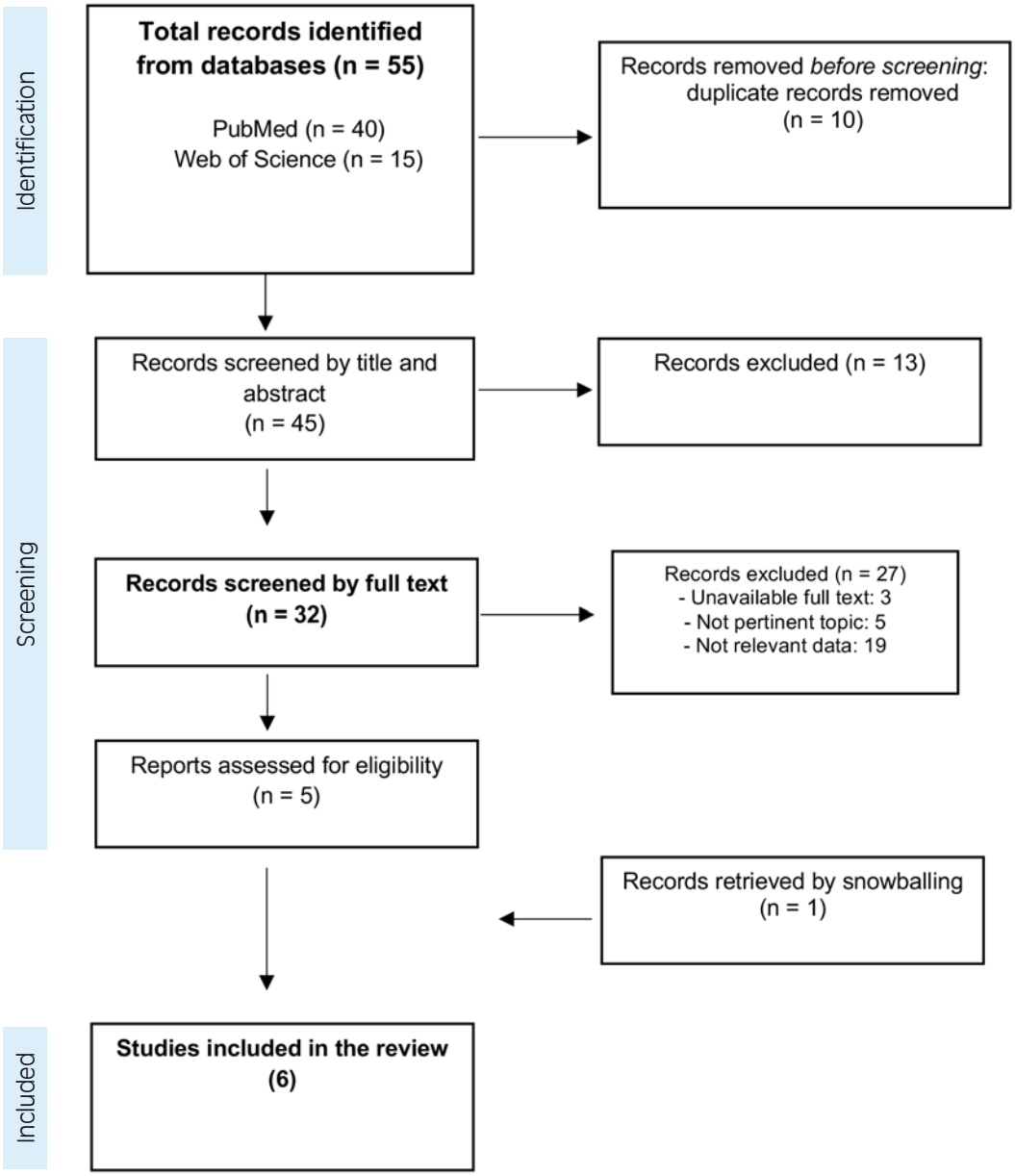
### Guideline statements

Insufficient and very heterogeneous data have emerged from the research of guideline statements pertinent to the management of BPH with IC.
Since 2003, the American Urology Association (AUA) guidelines have recommended treatment with IC, indwelling catheter, or stenting for patients who are not surgical candidates [33, 34].
In 2016, the Japanese guidelines for male lower urinary tract symptoms and BPH proposed the use of indwelling catheters and IC for the urinary retention care. Nonetheless, IC has been considered a viable alternative with a less common development of UTIs as compared to indwelling catheterization, and an earlier and more likely recovery of bladder function [15, 35].
Similarly, the "Korean guidelines for BPH underlined the advantages of IC compared with indwelling catheterizations in terms of quality of life, satisfaction, and adverse events such as symptomatic UTIs [35, 36]. The IC was also an optional strategy mentioned in the update of the 2018 Canadian Urological Association BPH guideline for the management of AUR secondary to the prostate enlargement [37].
Lastly, the recent French published consensus remarked how BPH patients should not be excluded from the scope of IC applications, as well as short-term bladder drainage, long-term bladder drainage, and bladder emptying in neurological disorder patients [25].

### Literature data

Overall, evidence on the use of IC in patients with a history of BPH is still scarce and related to pre- and post-operative observations. According to the current literature, in fact, IC is considered to manage retention while waiting for surgery and to promote recovery of the bladder after TURP or minimally invasive therapy. For example, Ghalayini et al. 2005 [26] emphasized the

Fig. 1. PRISMA statement flow diagram.




usefulness of a preliminary period of clean intermittent self-catheterization (CISC) before TURP to ensure a more effective recovery of post-operative bladder function when compared to BPH surgery alone. Among 41 BPH patients with a postvoid residual urine volume (PVR) greater than 300 ml, 17 (42%) (mean age: 67 years) were randomly assigned to immediate TURP and 24 (58%) patients (mean age: 69 years) were taught CISC for a period of 6 months prior to the surgical treatment. At 6 months post-surgery, there was a significant improvement in the International Prostate Symptom Score (IPSS) and quality-of-life for all the participants. However, the group of patients undergoing IC for 6 months prior to TURP had better bladder drainage, as shown from their pressure-flow curves. In particular, 19 (79%) patients from the CISC and 15 (88%) from the TURP group had a satisfactory symptomatic and urodynamic outcome after surgery and the use of CISC for 6-8 post-operative weeks significantly reduced PVR in men with poor emptying following TURP [26]. In contrast, Chung et al. (2012) [29], studying the optimal treatment for urinary retention of 78 men after photoselective vaporization of the prostate (PVP), reported not significantly different outcomes in those prior treated with intermittent self-catheterization (ISC) (n = 12) than patients managed by urethral catheterization (n = 61) and suprapubic catheterization (n = 5) [29].

Regarding the management of post-treatment urinary retention, Radomski et al. 1995 [38] described the need of IC for 38% of BPH patients immediately after pros-

tatectomy, whereof 10% had a continued need also after 3 months follow-up. This technique also resulted in a higher rate of spontaneous voiding than the IDC group (16 men; 56 *vs* 25%) and in a lower incidence of UTI (32 *vs* 75%) [38].
Similarly, Nishizawa et al. 2004 [28] described IC as an easy way to manage prostate swelling after minimal invasive surgery for BPH. Among the enrolled patients (n = 79) who underwent interstitial laser coagulation of the prostate, 43 patients experienced post-operative urinary retention, and 37 of these underwent CIC. The median post-operative catheterization time was 3 days (range 0 to 31), and all patients eventually became catheter free, suggesting that CIC and alpha-1 adrenergic blockade therapy could manage post-treatment urinary retention with a relatively short catheterization time.
A few years earlier, in 1999, also Stravodimos et al. [30] evaluated the effects of transurethral microwave thermotherapy (TUMT) on 78 men aged 52 to 85 years, with moderate to severe symptomatic BPH. After TUMT, 15 patients (23.8%) were taught CIC because of high PVR, and they continued it for a period of 1 to 8 weeks. However, this group of patients did not show a significant difference compared with the patients who did not need CIC in terms of symptom score at baseline and at 3 months [30].
Comparisons between intermittent and indwelling catheterization within the BPH cohort are scarce. Already in 1988, Furuhata et al. [39], observing the presence of pre- and post-operative bacteriuria in patients undergoing TURP, concluded that IC should be chosen in favor of an indwelling catheter in BPH patients with urinary retention or residual urine [39].
In 2001, Patel et al. [32] conducted a comparative trial between indwelling catheter (IDC) and CISC. Following a brief period of IDC, 34 men were taught how to use CISC, and they eventually showed a higher rate of spontaneous urination than the IDC group (16 men; 56 *vs* 25%). Moreover, the incidence of UTI was 32% in the CISC group and 75% in the IDC group. After TURP, patients who used CISC preferred it and had fewer complications than those who used IDC, with an incidence of 20% of UTI compared with 69% in the IDC group [32].
The use of IC may also be considered as a valid option when spontaneous voiding was not achieved after surgery treatments [31, 40].
For example, as reported by Djavan et al., at 3- and 6-months post TURP of 81 men aged 56 to 93 years old (mean age: 72 years), 11 of them (13%) were still unable to void or had high post-void residual urine volumes and required either an IDC (n = 1) or CIC (n = 10) [31].
In conclusion, specific studies on BPH treated with IC, and comparisons between intermittent and indwelling catheterization, are very few. Surgery is the most common and important treatment of BPH, relevant for approximately 25-61% of the patients, but this condition could however be relieved with IC, which is a safe, and effective treatment option for both short and long-term bladder management [24, 41, 42].

## Discussion

BPH has been demonstrated to be a progressive common disease in our ever-aging population, and subsequent LUTS can be debilitating above all for the elderly male [43].
The development of urinary retention is one of the most important manifestations of disease progression and is regarded generally as an indication for surgical intervention [44].
The gold standard for surgical treatment of BPH is represented by TURP, which has demonstrated significant symptom improvement and a durable success with a < 1% risk per year of requiring a repeat procedure [44]. However, in older adults, medical therapy is preferred to surgical intervention when possible [43].
Furthermore, emerging ambulatory, minimally invasive options, along with novel inpatient techniques, have been developed over the past decade and represent a promise for those that have failed medical therapy and are either not healthy enough or do not want the untoward side effects of TURP [23, 43].
Despite these benefits, post-operative and post-treatment prostate swelling is still a major problem associated with this clinical condition, causing obvious difficulties in emptying the bladder.
Since Lapides et al. reported the first experience with CISC, this method has been used widely to treat different types of bladder retention [45].
Commonly, IC is considered as the "gold standard" for individuals with bladder dysfunction caused by neurologic or non-neurologic causes [46].
However, limited recommendations are available from international learned societies exclusively on the usefulness of IC in BPH patients.
To identify the contemporary "real" management of BPH with IC, we performed a manual search of the main guidelines on this topic, but no clear international consensus was reached. In fact, the experts recommended the use of IC, whenever possible aseptic technique, as a standard treatment for all patients who are unable to empty their bladder [25, 37]. The review of the available published literature confirmed that the use of IC in BPH patients is still not well investigated. In fact, few specific BPH studies concerning IC have been identified from the search string.
The main findings of this review revealed that IC could be considered to manage retention while waiting for surgery, to promote recovery of the bladder after surgery and to manage the medical and surgical treatment fails [26, 30, 31, 38]. Furthermore, UTIs are among the greatest risks for people undertaking IC, although their reported incidence in these patients ranged from 20-to 32% and it is lower than that of indwelling catheters [32, 38]. Despite the lack of evidence, our results confirmed the IC as a safe, and effective treatment option for both short and long-term bladder management and, whenever possible, the first and preferred choice over urethral/suprapubic indwelling catheters [39].

In general, the choice of treatment for BPH is dependent on the patient's preference, treatment strategies, associated side effects or complications.

Some authors have also reported that patients found CISC to be more acceptable and manageable than other catheter types [32]. Amongst the main benefits of CISC on IDC, for example, is the convenience of not having an external device and the maintenance of sexual activity, as well as its relevant impact on aspects of quality of life or satisfaction [19, 28, 36].

Despite useful findings, several limitations should be considered in our review. The main ones are related to the lack of previous research studies on this topic and the resulting small sample of available articles. Moreover, substantial differences have been encountered between the articles and available guidelines because of the different purposes and the temporary publication years, making it difficult to compare and analyze them.

However, BPH and ensuing LUTS represent a significant health issue affecting millions of men and further research should be encouraged in order to fill the enormous knowledge gaps that exist.

Eventually, the present results emphasize the usefulness of IC in patients affected by BPH and increased evidence-based knowledge could guide and support the development of best practices as well as the most appropriate responses to patients' health needs [36].

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Chapter 5

# Economic impact of the intermittent catheterization

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## Introduction

This report is based on the adaptation to the Italian context of a model developed by the health economics consortium of the University of York (YHEC). All information within this report is derived from the YHEC model technical report. The adaptation process involved finding sources, tariffs, DRGs, drug acquisition prices, epidemiological data from the Italian context.

### Background

Injuries and conditions affecting the spinal cord can lead to impaired bladder function and therefore urinary retention, whereby an individual is unable to completely empty urine from the bladder. Urinary retention can have serious consequences if left untreated, such as urinary tract infections (UTIs), urinary incontinence, bladder damage and kidney damage, which can lead to kidney failure in some individuals [1].
Methods used to assist emptying of the bladder for those who are unable to void naturally are indwelling or suprapubic catheters (both left in place) and intermittent catheters (ICs) (removed once the bladder is empty) [2]. Catheters can be prescribed either for single use, or for reuse after a strict cleaning protocol. Clean intermittent catheterization is seen as the gold standard in care for managing urinary retention [3] and was found to be the safest method for bladder emptying, with the lowest potential for urological complications in patients with a spinal cord injury (SCI) [4]. Despite this, UTIs are still a common complication seen in catheter usage.
Frequent UTIs have a negative impact on health-related quality of life (HRQoL); they are at best a repeated inconvenience for patients, who already suffer with the more direct consequences of their neurological condition, and at worst they are life-threatening. The treatment of these infections places a substantial cost burden on the health system and contributes to the global issue of antibiotic resistance.
Intermittent catheters with a hydrophilic coating are seen to reduce some of the risk factors for UTIs, particularly by reduced trauma from repeated use of the product [5]. The hydrophilic coating allows for complete lubrication as the catheter is placed into the bladder, and so the withdrawal frictional force is lower than that of a conventional uncoated catheter. Furthermore, hydrophilic-coated catheters may lower the risk of long-term urethral complications that could otherwise be exacerbated by repeatedly inserting an uncoated catheter.
Two key populations who rely on intermittent catheters are people with multiple sclerosis (MS) and people with an SCI. Impaired bladder function is a consequence of the condition for many of these people, and so in turn is the need for catheterization.

### Overview of evaluation

The evaluation detailed in this report is in a population of MS and SCI individuals using ICs and takes a National Health Service (NHS) perspective, in the Italian setting. The decision problem assessed in the base case is described in Table I below.

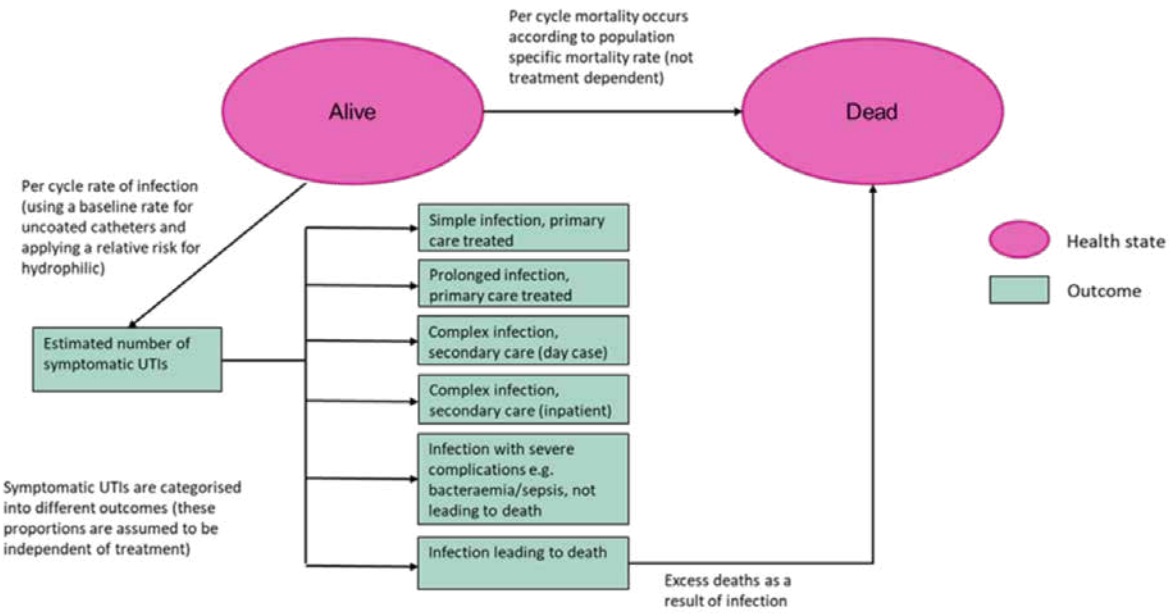
### Model structure

The model uses a Markov state-transition structure to predict the proportion of the cohort that remain alive in each cycle, based on the probability of mortality which varies as the cohort ages. The modelling of UTIs, the main clinical driver of the model, is done by applying incidence rates to the living cohort with a treatment ef-

Tab. I. Summary of the decision problem.

| Model element | Description |
|---|---|
| Population | MS and SCI individuals who use ICs |
| Perspective | Italian NHS |
| Model design | State transition cohort model |
| Discount rate | 3.0% per annum, for both costs and benefits |
| Intervention | Hydrophilic-coated intermittent catheters |
| Comparator | Uncoated intermittent catheters |
| Cycle length | 1 year (with half-cycle correction applied) |
| Time horizon (years) | Lifetime |
| Key outcomes of the model | Total costs, total quality-adjusted life years (QALYs), total life years (LYs), total numbers of events, incremental cost-effectiveness ratio (ICER), net monetary benefit (NMB) |

Fig. 1. Model structure.




fect applied for hydrophilic-coated catheters. The model structure is depicted in Figure 1.

UTIs occurring in the model are stratified into six categories, presented in Table II in increasing order of severity. There is no impact of catheter type on the breakdown of UTIs, that is, one type of catheter is assumed not to cause more severe infections than another. Each UTI outcome is associated with a different set of resource use and HRQoL outcomes.

The model utilises annual cycles, meaning that movements between health states (Alive, or Dead) only occur at the end of each year. The use of discrete cycles of time is a common feature of health economic models. However, it is of course not realistic that patients would only die at discrete time points, and in fact on average deaths would occur at the midpoint of each cycle. To address this, a half-cycle correction is applied in the model calculations. For each cycle, mean costs and HRQoL utilities are assigned to the living cohort. The proportion of the cohort in the Dead state do not accrue costs and QALYs. The model utilises a lifetime horizon, reflected in an arbitrarily large value of 100 years. A lifetime horizon is recommended when modelling a chronic condition, to ensure that all differences in costs and benefits are captured in the evaluation.

### Structural assumptions in the model

As with any economic model, structural assumptions were required. These are summarised below and should be taken heed of when interpreting the results:

- recurrent UTIs are not factored in explicitly (the modelling is done at a cohort-level and so does not track patient history of previous UTIs). It was deemed more meaningful in terms of costs and outcomes to stratify UTIs according to their severity, rather than increase model complexity by considering recurrent UTIs separately. The incidence rates applied do implicitly capture recurrent UTIs, but the costs and QALYs do not differentiate;
- asymptomatic UTIs are not considered, as it is assumed that their cost and HRQoL impact is minimal. Other complications of catheterization were also not considered;
- the underlying condition of the cohort is not modelled; it is assumed that the effect on HRQoL and mortality associated with MS or an SCI is constant over time. This is a necessary simplifying assumption and does not substantially bias the incremental results;
- costs and outcomes are assigned based upon the ultimate severity of each UTI event. That is, a UTI that is at first simple but in time becomes life threatening, would be modelled as if the patient were in secondary care receiving treatment for a severe UTI from the beginning. This approach differs from other models where the cohort can transition from one UTI state to a worse one to reflect progression of the infection;
- there is no treatment effect on the breakdown of UTIs (i.e. one type of catheter does not cause more severe UTIs than another).

### Health economic inputs

The economic model takes a Italian perspective in the base case, focusing on the NHS related costs. Table III presents the discount rates and cost-effectiveness threshold as used in the model under the current UK perspective. Discounting is not applied to costs and QALYs during the first annual cycle.

Tab. II. Description of UTI outcomes.

| Outcome | Description |
|---|---|
| Simple infection treated in primary care | These infections are successfully treated in primary care with one round of antibiotics and do not require any secondary care. HRQoL impact is small. |
| Prolonged infection treated in primary care | These infections are not successfully treated with the first course of antibiotics and require slightly more health care resource use. HRQoL impact is small (but prolonged, compared to the simplest infections). |
| Complex infection treated in day case secondary care | These infections have some complexities requiring secondary care assessment/treatment but do not require an inpatient stay. HRQoL impact is larger than for those treated in primary care, but is still relatively minor. |
| Complex infection treated in day case secondary care | These infections require a stay in secondary care (e.g. for treatment with IV antibiotics). Therefore they are much more costly than previous outcomes. HRQoL impact is still minor but is prolonged. |
| Infection with severe complications, not leading to death | These are the infections which escalate to severe complications such as sepsis. These infections are more costly and are quite impactful in terms of HRQoL. |
| Infection leading to death | These are almost twice as costly and almost twice as impactful on HRQoL as the previous UTI category, but the main difference is that these infections are ultimately fatal and contribute to the overall mortality in the model. |

Tab. III. Economic parameters.

| Economic parameters | Base case input | Source |
|---|---|---|
| Discount rate - costs | 3.0% | AIFA guidelines |
| Discount rate - benefits | 3.0% | |
| Cost-effectiveness threshold (per QALY gained) | 30.000 € | |

## Cohort characteristics

The cohort being modelled is long-term catheter users who suffer from either an SCI or MS. A 50:50 split between SCI and MS is taken to represent the cohort in the base case.

The model is populated with a population-specific starting age for each population, and a weighted average is calculated based on the population breakdown to obtain a suitable starting age for the cohort. The population-specific starting ages are recorded in Table IV.

Similarly, proportion male is calculated by taking a weighted average of the population-specific percentages with the population breakdown. The population-specific percentages for proportion male are outlined below in Table V.

## Clinical parameters

The baseline annual rate of UTIs for uncoated catheter users is used to predict the number of UTIs that occur per cycle. The model uses a relative rate of infection to capture the expected reduction in number of UTIs when hydrophilic-coated catheters are used as an alternative. These inputs are recorded in Table VI alongside the calculated absolute annual rate of UTIs when hydrophilic-coated catheters are used.

The model stratifies UTIs according to degree of severity, with the six severity categories described in Table II. Table VII indicates the percentage of UTIs that are associated with each outcome. The outcomes are listed in ascending order of severity, with costs and HRQoL impacts assigned accordingly.

Tab. IV. Population-specific starting age.

| Cohort characteristics | Base case input | Source |
|---|---|---|
| Spinal cord injury | 40 | National Spinal Cord Injury Statistical Centre (2011) [6]. |
| Multiple sclerosis | 54.4 | Mahajan et al. (2013) [7] ~ Table V: average age of catheter users with MS. |

Tab. V. Population-specific proportion male.

| Cohort characteristics | Base case input | Source |
|---|---|---|
| Spinal cord injury | 80% | National Spinal Cord Injury Statistical Centre (2011) [6]. |
| Multiple sclerosis | 30% | Mahajan et al. (2013) [7] ~ This estimate was derived based on information on characteristics of the average person with MS, combined with data on catheter usage. 24.6% of respondents were male, but catheter use was more prevalent in men compared with women (31.5% compared with 24.2%). So it can be estimated that 7.75% of MS patients are male and use a catheter, compared with 18.25% of MS patients being female and using a catheter. Therefore there is an estimated ratio of 0.3 male catheter users with MS: 0.7 female catheter users with MS. |

Tab. VI. Base case annual rate of UTIs.

| Clinical parameters | Base case input | Source |
|---|---|---|
| Baseline rate (with comparator) | 3.27 | Weighted average of rates from four studies ~<br>Cardenas et al. (2011) [8], [n = 114, annual rate = 5.76]<br>Cardenas et al. (2009) [9], [n = 23, annual rate = 1.68]<br>De Ridder et al. (2005) [10], [n = 61, annual rate = 4.56]<br>Woodbury et al. (2008) [11], [n = 502, annual rate = 2.62] |
| Relative rate of infection (with intervention) | 0.84 | Rognoni et al. (2017) [12] |
| Absolute rate (with intervention) | 2.75 | Calculated by multiplying baseline rate (with comparator) by relative rate (with intervention) |

Tab. VII. Breakdown of UTIs.

| Outcome | Base case input | Source |
|---|---|---|
| Simple infection, treated in primary care | 50.0% | Assumptions informed and validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck - in meetings dated 07.12.21 and 09.12.21 respectively) |
| Prolonged infection, treated in primary care | 25.0% | |
| Complex infection requiring day case in hospital | 3.0% | |
| Complex infection requiring inpatient stay in hospital | 17.0% | |
| Infection with severe complications, not leading to death | 4.25% | |
| Infection leading to death | 0.75% | |

### Mortality

Age and gender-specific all-cause mortality rates were sourced from the Italian National Institute of Statistics (ISTAT) life Tables [13]. The gender-specific rates were weighted according to the cohort gender split to produce a mortality rate, by age, for a general population cohort of this specification. To adjust these rates to account for the increased risk of mortality in people with SCI and MS, standardised mortality ratios (SMRs) of 2.07 for SCI [14] and 2.61 for MS [15], as outlined in Table VIII, were applied multiplicatively to the general population estimates. Rates were converted into probabilities via standard formulae. From the estimated rates for each population, the model calculates weighted averages based on the population breakdown to determine the final mortality probabilities for use in the calculations.

General mortality was assumed to be treatment-independent, however excess mortality as a result of UTI complications is captured by the model. Whilst treatment effect on mortality is expected to be small, there are a small proportion of UTIs that may lead to death. Therefore, a decrease in the number of UTIs caused by catheterization results in a slight decrease in mortality predicted by the model.

### Health-related quality of life

The population norms used for age and gender-adjustment were sourced from Kind et al. (1999) [16]. To capture the decrease in utility associated with each condition, the model applies utility decrements to both the SCI and MS populations, as outlined in Table IX below. These utility decrements are subtracted from the general population norms to obtain population-specific utilities. The model then calculates weighted averages based on the population breakdown to calculate utility values for the modelled cohort.

An additional, permanent utility decrement is applied to uncoated catheter users (and not to hydrophilic-coated catheter users), to reflect patient preference. See Table X. This decrement was elicited through a time trade-off (TTO) study by Averbeck et al. (2018) [19], and reflects the perceived value of fewer steps (no need to lubricate) and improved comfort associated with a hydrophilic-coated catheter. It does not reflect the reduction in UTIs, and so there should not be any double counting of HRQoL benefit within the model.

In addition to the long-term utilities described above, short-term utility decrements are applied for each UTI outcome. These are presented in Table XI. To estimate the QALY impact of each event, these decrements are each multiplied by a duration, given in Table XII. Quality-adjusted life day (QALD) decrements have been recorded for ease of interpretation and are presented in Table XIII. The QALD decrements are converted back to QALY decrements in the calculations, to align with the annual cycles.

### Unit costs and resource use

There are two main categories of costs in the model: Costs of catheterization, and costs of treating UTIs.

#### *Costs of catheterization*

A list of the most commonly used hydrophilic-coated catheters for each sex was provided by Coloplast, with the market share associated with each catheters in the Italian context. Costs of the single catheter were provided as well by the company. The unit costs for the male and female products are presented in Table XIV and Table XV respectively. A simple average hydrophilic-coated catheter cost was calculated for each sex.

When costing uncoated catheters, a list of most commonly used brands was not available. Thus, we are assuming an average unit cost of uncoated catheters equals

Tab. VIII. Standardised mortality ratios.

| Population | Base case input | Source |
|---|---|---|
| SCI | 2.07 | Chamberlain et al. (2015) [14] ~ An SMR of 2.07 was reported in Figure 5. This reflects the population with paraplegia from SCI. |
| MS | 2.61 | Smyrke et al. (2021) [15] ~ This source was chosen over others because it is up to date with most recent data. |

Tab. IX. Utility decrements (by population).

| Population | Base case input | Source |
|---|---|---|
| Spinal cord injury (SCI) catheter users | 0.08 | Bermingham et al. (2013) [17] ~ The utility for SCI for a cohort of catheter users aged 40 years old with 80% male was provided by the above (0.831).<br>The utility norm for a cohort aged 40 years old with 80% male was obtained from the model (0.91), and 0.831 was subtracted from this to estimate the utility decrement for SCI catheter users. |
| Multiple sclerosis (MS) catheter users | 0.33 | Orme et al. (2007) [18] ~ Utility for EDSS 5 (reflects MS of middling severity) is assumed to be averagely representative of a MS patient with bladder impairment. This takes a value of 0.518. The study was carried out in a population with mean age 51.4 so a decrement was calculated by subtracting 0.518 from the utility norm of a 51 year old (0.845).<br>It is assumed that this utility accounts for catheter usage and so no further utility decrement was applied for catheterization. |

Tab. X. Utility decrement associated with uncoated catheters.

| Population | Base case input | Source |
|---|---|---|
| Uncoated catheter users | 0.017 | Averbeck et al. (2018) [19] ~ Table III, second row.<br>It is a modeller assumption that the population-specific estimate for SCI catheter users relates to the use of hydrophilic-coated catheters as opposed to uncoated (we cannot access the full papers referenced by Bermingham et al to confirm/deny this assumption). Therefore, this value is applied as a decrement for uncoated catheters, rather than as an additional benefit for hydrophilic-coated catheters. |

Tab. XI. Utility decrements by UTI type.

| Outcome | Base case input | Source |
|---|---|---|
| Simple infection, treated in primary care | 0.10 | Assumption, validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck, in a meeting dated 16.09.21) |
| Prolonged infection, treated in primary care | 0.10 | |
| Complex infection requiring day case in hospital | 0.15 | |
| Complex infection requiring inpatient stay in hospital | 0.15 | |
| Infection with severe complications, not leading to death | 0.17 | NICE [TA370] (2015) [20] ~ Note this decrement is based on small patient numbers |
| Infection leading to death | 0.17 | Assumption, validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck, in a meeting dated 16.09.21) |

Tab. XII. Duration of utility decrements by UTI type (days).

| Outcome | Base case input | Source |
|---|---|---|
| Simple infection, treated in primary care | 7 | Assumption, validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck, in a meeting dated 16.09.21) |
| Prolonged infection, treated in primary care | 14 | |
| Complex infection requiring day case in hospital | 14 | Assumption, validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck, in a meeting dated 16.09.21) |
| Complex infection requiring inpatient stay in hospital | 28 | Assumption, validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck, in a meeting dated 16.09.21) |
| Infection with severe complications, not leading to death | 37 | Rognoni et al. (2017) [12] ~ Based on DRG data in Italy |
| Infection leading to death | 65 | Rognoni et al. (2017) [12] ~ Based on DRG data in Italy |

to 1,53 € for both genders. OptiLube sterile lubricating jelly (sachet) cost was also estimated (0,16 €). These unit costs are presented in Table XVI.

Users of both catheter types are estimated to use five catheters per day, as presented below in Table XVII. The model user can run distinct values through the model if they wish. However, extreme values are not recommended as the clinical parameters reflect this frequency of use and may be invalid for modelling a population who catheterise more/less frequently. A range of

Tab. XIII. Quality-adjusted life day (QALD) decrements.

| Outcome | Base case input | Source |
|---|---|---|
| Simple infection, treated in primary care | 0.70 | Utility decrements multiplied by durations |
| Prolonged infection, treated in primary care | 1.40 | |
| Complex infection requiring day case in hospital | 2.10 | |
| Complex infection requiring inpatient stay in hospital | 4.20 | |
| Infection with severe complications, not leading to death | 6.327 | |
| Infection leading to death | 11.115* | |

* The true impact of an infection leading to death includes the QALYs lost from premature mortality. The decrement presented here is intended to capture the loss of HRQoL during the event.

Tab. XIV. Hydrophilic catheter unit costs ~ male products cost per item.

| Item | Base case input | Market share | Source |
|---|---|---|---|
| SpeediCath Compact Uomo | € 1.77 | 24% | Coloplast |
| SpeediCath Standard | € 1.77 | 18% | |
| SpeediCath Flex/Flex Pocket | € 1.84 | 9% | |
| Wellspect (Lofric Origo) | € 1.66 | 17% | |
| Teleflex (Liquick X-Treme, Liquik Base) | € 1.93 | 12% | |
| Hollister (Vapro Pocket) | € 1.79 | 0% | |
| Catheters with integrated bag | € 3.56 | 20% | |

Tab. XV. Hydrophilic catheter unit costs ~ female products cost per item.

| Item | Base case input | Market share | Source |
|---|---|---|---|
| SpeediCath Compact Donna | € 1.73 | 13.5% | Coloplast |
| SpeediCath Compact Plus | € 1.60 | 10.6% | |
| SpeediCath Standard | € 1.75 | 19.7% | |
| SpeediCath Compact Eve | € 1.83 | 11.7% | |
| Wellspect (Lofric Sense) | € 1.89 | 25.4% | |
| Teleflex (Liquik Pure/Base/X-Treme) | € 1.96 | 3.1% | |
| Bbraun (Actreen Mini) | € 1.65 | 3.5% | |
| Catheters with integrated bag | € 3.39 | 12.4% | |

Tab. XVI. Uncoated catheter unit costs ~ male and female products cost per item.

| Item | Base case input | Source |
|---|---|---|
| Average uncoated catheter | 1.53 € | Bermingham et al. (2013) [17] ~ 2013 cost of £1.19 was inflated to a 2019/20 cost using the hospital & community health services (HCHS) inflation index |
| OptiLube Sterile Lubricating Jelly (sachet) | 0.16 € | Transparency list AIFA [21] |

Tab. XVII. Number of items used (per patient per day).

| Item | Base case input | Source |
|---|---|---|
| Hydrophilic-coated catheters | 5 | Woodbury et al. (2008) [11]. |
| Uncoated catheters and lubricant | 5 | |

Tab. XVIII. Summary ~ annual cost of catheterization.

| Treatment arm | Base case input | Source |
|---|---|---|
| Hydrophilic-coated catheter users | 3.774 € | Calculated from unit costs and resource use |
| Uncoated catheter users | 3.086 € | |

plausible values (whilst still assuming equivalence in usage between the two catheter types) is examined in the sensitivity analysis.

Unit costs are combined with the frequency of catheter use to produce an average cost of catheterization for each treatment arm. These summary costs are presented in Table XVIII.

*Costs of treating UTIs*

For infections treated in primary care, a micro-costing approach was taken whereby the costs of each element of resource use (antibiotics, GP time, testing) were sourced and used to calculate an overall cost for each type of infection.

Expert opinions were used to determine appropriate antibiotic dosage for each of the listed antibiotics for the treatment of a UTI. Transparency lists from Italian Medicine Agency (AIFA) was used as source to estimate the treatment cost. The antibiotic costs for use in the model were calculated by considering the dosage information in combination with the sourced unit costs, and these calculated costs are recorded in Table XIX.
An equal split in use of Nitrofurantoin, Trimethoprim and Amoxicillin was assumed for first-line antibiotic treatment. In addition, an equal split in use of Pivmecillinam, Cefalexin, Co-amoxiclav and Ciprofloxacin was assumed for second-line antibiotic treatment.
Cost per course of antibiotics is calculated for each treatment line by taking an average of the unit costs, and these costs are recorded below in Table XX.
Unit costs for other healthcare resources associated with UTI treatment in primary care are listed below in Table XXI and were extrapolated from the Italian nomenclature for specialist outpatient services.
Clinical input was sought to obtain the resource use frequencies presented in Table XXII. It was reasoned that a simple infection would require a face-to-face consultation with a GP, a prescription for one of the first-line antibiotic options, a culture & susceptibility test to confirm appropriateness of treatment, and a final follow up with the GP over the phone. Prolonged infections would require an additional course of antibiotics (a second-line option) as well as an additional face-to-face GP consultation. Italy does not provide a fee for telephone consultation with the GP. For this reason, the fee for the cost of the visit equal to € 20.66 was used. These frequencies were multiplied with the corresponding unit costs and summed to produce a total cost of treating each type of infection.
For infections treated in secondary care, composite costs of treatment (incorporating all elements of resource use) were sourced for use in the model. These are presented, alongside the summary costs of the primary care treated infections, in Table XXIII.
The Italian DRG reference costs were used where these could be aligned with the description of outcomes in the model. For the cost of a fatal infection, an assumption was made to maintain proportionality with the HRQoL outcomes.

## Results

### Deterministic base case results

The deterministic base case results are summarised in Table XXIV below. These results relate to a lifetime time horizon (i.e. predicting outcomes from the

**Tab. XIX.** Antibiotic costs for seven-day course.

| Antibiotic | Base case input | Source |
|---|---|---|
| Nitrofurantoin | € 4.08 | AIFA Transparency list [21] |
| Trimethoprim | € 2.48 | |
| Amoxicillin | € 0.93 | |
| Pivmecillinam | € 3.77 | |
| Cefalexin | € 6.34 | |
| Co-amoxiclav | € 3.75 | |
| Ciprofloxacin | € 5.01 | |

**Tab. XX.** Summary: average cost per course of antibiotics.

| Line of treatment | Base case input | Source |
|---|---|---|
| First line | € 2.50 | Calculated |
| Second line | € 4.72 | |

**Tab. XXI.** Healthcare-related unit costs.

| Resource | Base case input | Source |
|---|---|---|
| Culture & susceptibility testing | € 9.56 | "Nomenclatore delle prestazioni ambulatoriali specialistiche" [22] |
| Face-to-face GP appointment | € 20.66 | |
| Phone consultation GP appointment | € 20.66 | |

**Tab. XXII.** Healthcare-related resource use for primary care treated infections.

| Resource | Simple infection | Prolonged infection | Source |
|---|---|---|---|
| Courses of first-line antibiotics (seven days) | 1 | 1 | Assumption, validated by clinical opinion by YHEC (Nikesh Thiruchelvam and Marcio Averbeck, in a meeting dated 16.09.21) |
| Courses of second-line antibiotics (seven days) | 0 | 1 | |
| Rounds of culture & susceptibility testing | 1 | 1 | |
| Number of face-to-face GP consultations | 1 | 2 | |
| Number of GP phone consultations | 1 | 1 | |

Tab. XXIII. Cost of treatment by UTI type (per event).

| Outcome | Base case input | Source |
|---|---|---|
| Simple infection, treated in primary care | € 53 | Calculated based on micro-costing (included antibiotics, GP time and testing) |
| Prolonged infection, treated in primary care | € 79 | |
| Complex infection requiring day case in hospital | € 286 | DRG 321 [23] |
| Complex infection requiring inpatient stay in hospital | € 1.883 | DRG 321 [23] |
| Infection with severe complications, not leading to death | € 2.701 | DRG 320 [23] |
| Infection leading to death | € 4.754 | Calculated |

starting age all the way through to death of the entire cohort). They are discounted at 3.0% per annum. Life years are presented undiscounted for more intuitive interpretation.

These results show that hydrophilic-coated catheters are more expensive overall, but are also associated with more QALYs over a patient's lifetime. The life years per patient are greater for the hydrophilic-coated catheter arm, a result that is driven by a reduction in infection-related fatalities.

The ICER is 14.275 € per QALY gained, representing the additional cost that is associated with one additional QALY in this comparison. This result is comfortably below the commonly used cost-effectiveness threshold in Italy of 30.000 € per additional QALY gained.

Alternatives to the ICER are NMB and NHB. These two statistics represent the net benefit of hydrophilic-coated catheters compared with uncoated catheters, when all benefits are converted into either monetary units or QALYs, respectively. They have been calculated on the basis of a willingness to pay of 30.000 € per additional QALY. These results reflect the positive cost-effectiveness result, as they are both positive values.

### Cost breakdown

A breakdown of discounted costs, again over a patient's lifetime, is presented in Table XXV. The breakdown shows that hydrophilic-coated catheters are more expensive in terms of the product cost, but that much of this additional cost is offset by cost savings in healthcare, due to reduced frequency of infections. This information is presented graphically in Figure 2.

### QALY breakdown

For completeness, a breakdown of QALYs predicted over a patient's lifetime is also presented, in Table XXVI. It can be deduced that the utility gain from reduced infections is minimal, and that the vast majority of incremental gained QALYs for hydrophilic-coated catheter users come from the baseline utility applied to the living cohort. This benefit is driven by two elements of the treatment effect: the utility decrement that is applied to the uncoated catheter arm to account for patient preference, and the survival benefit attributable to reduced infection-related fatalities.

### Counts of clinical outcomes

A breakdown of the clinical outcomes predicted over a patient's lifetime is presented in Table XXVII. These results are not discounted.

The number of events avoided by using hydrophilic-coated catheters rather than uncoated catheters, per patient's lifetime, is substantial. In total, seven infections are avoided. For each UTI outcome, a cost per event avoided is presented. This is a ratio of the total incremental cost of hydrophilic-coated catheters (from Table V.1) to the number of events avoided.

The number needed to treat (NNT) represents the number of patients who would have to be prescribed hydrophilic-coated catheters rather than uncoated catheters in order to avoid one event, over a lifetime horizon.

### Probabilistic results

The PSA was run with 10,000 iterations. The probabilistic results are summarised in Table XXVIII. The mean results are relatively robust to parameter uncertainty. In 89% of iterations, hydrophilic-coated catheters were found to be cost-effective.

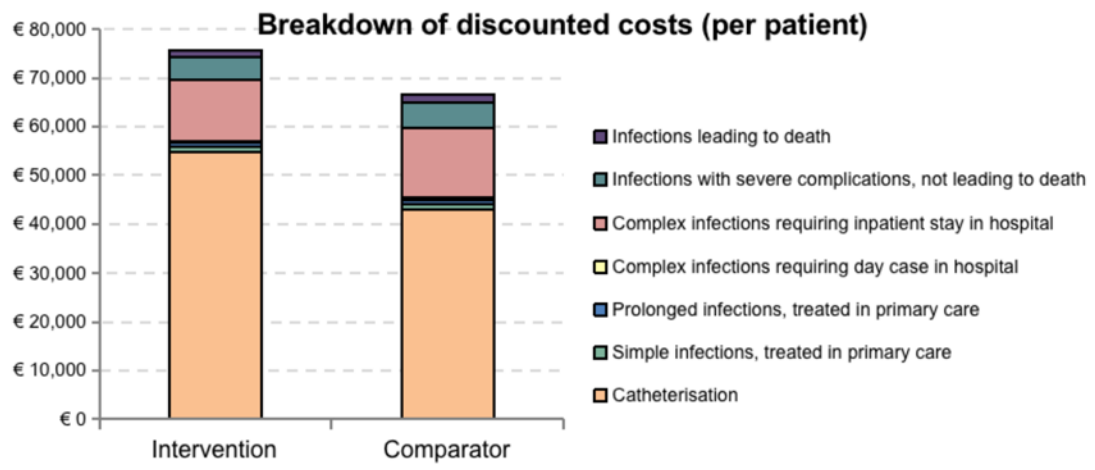
The results of the PSA are also presented graphically, in a cost-effectiveness plane (Fig. 3) and a CEAC (Fig. 4).

The cost-effectiveness plane is a plot of the incremental costs and incremental QALYs predicted by each iteration of the PSA. The cloud surrounding the base case estimate illustrates the uncertainty in results attributable to parameter uncertainty. The dashed line represents a cost-effectiveness threshold of 30.000 € per additional

Tab. XXIV. Summary of base case results.

| | Hydrophilic | Uncoated | Incremental |
|---|---|---|---|
| Cost per patient (discounted) | € 75.677 | € 66.670 | € 9.007 |
| QALYs per patient (discounted) | 8.62 | 7.99 | 0.63 |
| Life years per patient (undiscounted) | 20.65 | 19.56 | 1.10 |
| **Incremental cost effectiveness ratio (ICER)** | | | **€ 14.275** |
| **Net monetary benefit (NMB) per patient** | | | € 3.612 |
| **Net health benefit (NHB) per patient** | | | 0.18 |

Fig. 2. Breakdown of discounted costs.




Tab. XXV. Breakdown of discounted costs.

| | Hydrophilic | Uncoated | Incremental |
|---|---|---|---|
| Catheterization | € 54.740,04 | € 42.825,24 | € 11.914,79 |
| Simple infections, treated in primary care | € 1.063,33 | € 1.210,99 | -€ 147,66 |
| Prolonged infections, treated in primary care | € 784,41 | € 893,34 | -€ 108,93 |
| Complex infections requiring day case in hospital | € 341,83 | € 389,30 | -€ 47,47 |
| Complex infections requiring inpatient stay in hospital | € 12.753,40 | € 14.524,46 | -€ 1.771,05 |
| Infections with severe complications, not leading to death | € 4.573,41 | € 5.208,52 | -€ 635,11 |
| Infections leading to death | € 1.420,45 | € 1.617,70 | -€ 197,26 |
| **Total** | **€ 75.676,87** | **€ 66.669,56** | **€ 9.007,32** |

Tab. XXVI. Breakdown of discounted QALYs.

| | Hydrophilic | Uncoated | Incremental |
|---|---|---|---|
| Baseline (accrued by living cohort) | 8.82 | 8.21 | 0.60 |
| Simple infections, treated in primary care | -0.04 | -0.04 | 0.01 |
| Prolonged infections, treated in primary care | -0.04 | -0.04 | 0.01 |
| Complex infections requiring day case in hospital | -0.01 | -0.01 | 0.00 |
| Complex infections requiring inpatient stay in hospital | -0.08 | -0.09 | 0.01 |
| Infections with severe complications, not leading to death | -0.03 | -0.03 | 0.00 |
| Infections leading to death | -0.01 | -0.01 | 0.00 |
| **Total** | **8.62** | **7.99** | **0.63** |

Tab. XXVII. Counts of clinical outcomes (per patient).

| | Hydrophilic | Uncoated | Events avoided by hydrophilic | Cost per event avoided | Number needed to treat (NNT) |
|---|---|---|---|---|---|
| Simple infections, treated in primary care | 28.4 | 32.0 | 3.6 | € 2.495,28 | 1 |
| Prolonged infections, treated in primary care | 14.2 | 16.0 | 1.8 | € 4.990,56 | 1 |
| Complex infections requiring day case in hospital | 1.7 | 1.9 | 0.2 | € 41.587,97 | 5 |
| Complex infections requiring inpatient stay in hospital | 9.6 | 10.9 | 1.2 | € 7.339,05 | 1 |
| Infections with severe complications, not leading to death | 2.4 | 2.7 | 0.3 | € 29.356,21 | 4 |
| Infections leading to death | 0.43 | 0.48 | 0.05 | € 166.351,86 | 19 |

QALY gained, and any points below this threshold are cost-effective results.

The CEAC plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective at that threshold on the vertical axis. It is based upon the proportion of PSA iterations that would be considered cost-effective results at various thresholds.

Tab. XXVIII. Summary of probabilistic results.

| | Hydrophilic | Uncoated | Incremental |
|---|---|---|---|
| Average cost per patient (discounted) | € 75.267 | € 72.037 | € 3.230 |
| Average QALYs per patient (discounted) | 8.03 | 7.48 | 0.56 |
| **Average incremental cost effectiveness ratio (ICER)** | | | **€ 5.803** |
| **Average net monetary benefit (NMB) per patient** | | | **€ 7.902** |
| **Probability of cost-effectiveness** | | | **89.0%** |

## Conclusion of the evaluation

The evaluation found hydrophilic-coated catheters to be cost-effective when compared with uncoated catheters. This result was largely robust to parameter uncertainty when assessed probabilistically Strengths of the Evaluation.

The project incorporated informal expert elicitation at several key points during model development by YHEC. Firstly, the proposed model structure was presented to clinical KOLs to ascertain how well it reflected the clinical pathway. All economic models are simplifications of reality, but it was deemed that this *de novo* model was appropriate in its assumptions and that its structure allowed the main differences in cost and benefits to be captured.

In addition to validation of the model structure, the KOLs also participated in validating the key model inputs. As with structural limitations, some parameter uncertainty is inevitable in economic models. Where evidence was scarce and modeller assumptions were required, these assumptions were, wherever possible, confirmed with the KOLs to be clinically plausible.

The parameter uncertainty in this model was largely present in parameters that weren't considered key drivers of the incremental results, and thus was relatively unproblematic for determining cost-effectiveness. For example, the magnitude of treatment effect (reduction in UTIs) was sourced from a network meta-analysis, the gold standard of evidence. As a result, the cost-effectiveness results in this report can be presented with a fair amount of confidence. Indeed, the results of the PSA would suggest that hydrophilic-coated catheters are a cost-effective intervention in 67.2% of simulations.

Fig. 3. Cost-effectiveness plane.

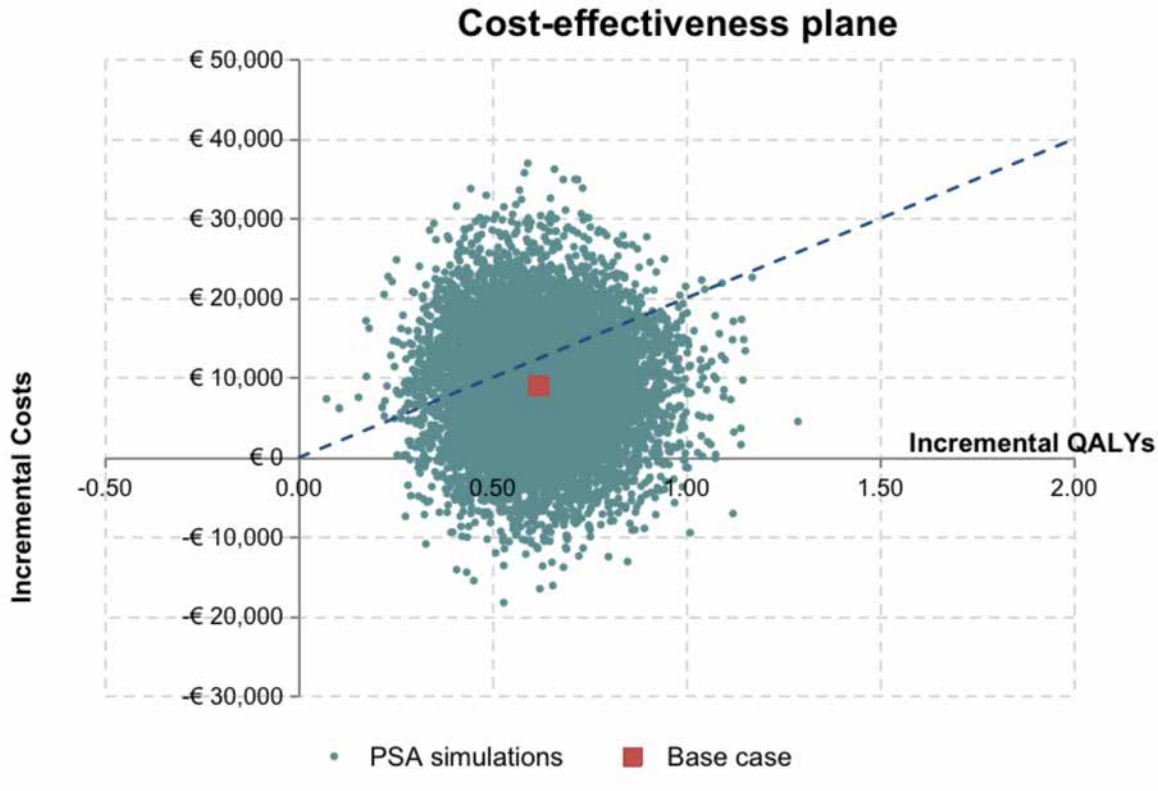


Fig. 4. Cost-effectiveness acceptability curve (CEAC).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Chapter 6

# Technical characteristics of LUJA and the Italian regulation context

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## Bladder catheter

The bladder catheter is a latex or silicone drainage that is introduced into the bladder through the urethra to facilitate the outflow of urine and can be used for diagnostic, therapeutic or evacuation purposes. Since catheter use is associated with an increased risk of urinary tract infections, it should be limited to cases where no alternative is feasible (e.g. in cases of urinary tract obstruction or urinary retention, neurological bladder dysfunction, surgery, urinary incontinence, etc.). Specialised personnel must perform catheter insertion [1].
Bladder catheters are differentiated into urethral and suprapubic catheters; while urethral bladder catheters are divided into permanent and intermittent, the suprapubic catheter can only be permanent [2].

### Intermittent urinary bladder catheters

This type of urethral catheter is disposable, sterile and pre-lubricated for easy insertion. According to international guidelines, the use of intermittent catheterization is recommended for people with bladder emptying dysfunction; bladder emptying is recommended 4-5 times a day [3]. Such catheters are in fact inserted several times a day for the duration to drain the bladder and then are removed [4].
The intermittent urinary bladder catheter is primarily intended for self-catheterization: the patient must be instructed on how to insert the catheter himself. Specifically, the catheter is inserted into the bladder through the urethra: one end of the catheter may be kept open to allow drainage into the toilet or connected to a urine collection bag, while the other end is inserted into the bladder through the urethra allowing urine to flow out. The catheter is removed after the flow of urine is interrupted. A new catheter is used for each insertion [4].
There are two main types of catheters used during intermittent catheterization: non-hydrophilic catheters (uncoated) and hydrophilic catheters (coated). The latter have a slippery surface that facilitates insertion and removal of the catheter [5].

### Clean intermittent catheterization (CIC)

Intermittent self-catheterization is an operation to empty the bladder and is intended to prevent urine retention or incontinence by avoiding the discomfort caused by the use of a permanent catheter for the patient, while also reducing the risk of infection related to the presence of a permanent catheter. Intermittent self-catheterization refers to the insertion of a bladder catheter into the urethra in an autonomous manner so that the bladder can be completely emptied. Intermittent catheterization is a manoeuvre with a high risk of infection (Tab. I): since the urethra and bladder are sterile, the operation must be performed while maintaining a high level of cleanliness [6]. The CIC should be performed at regular intervals throughout the day, based on the person's fluid intake. Guidelines recommend performing the procedure every 4 to 6 hours, but if the urine volume is greater than 400-500 ml, it should be performed more frequently or the patient's fluid intake should be reduced [3].

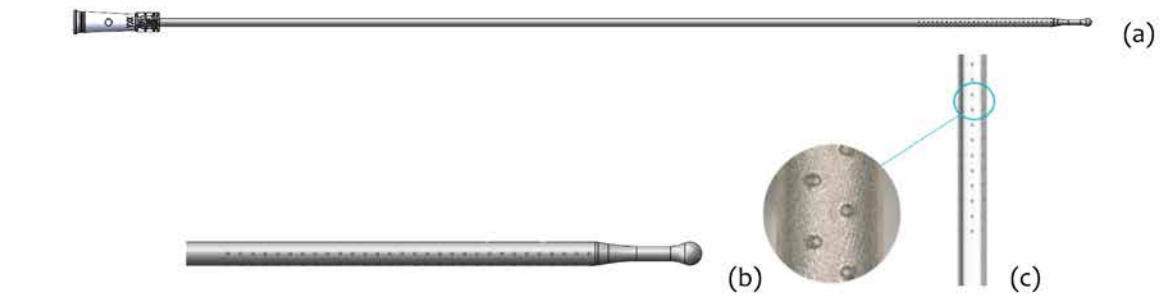
## Luja medical device

The Luja device is a male catheter intended for intermittent catheterization and intermittent dilatation of the urethra. The device is sterile, single-use, ready-to-use and consists of a hydrophilic coating (Coloplast, 2021).
In particular, the device is indicated for urinary retention and/or post-void residual volume due to bladder dysfunction. The device is primarily intended for self-catheterization, but can also be used by healthcare professionals and staff.
The device has a flexible tip that facilitates passage through the sphincter into the urethra. It consists of micro-holes that create a drainage area, allowing urine to flow from the bladder through the catheter. The sleeve ensures sterility when the catheter is removed from the primary package and allows maintaining optimal hygiene in each phase of catheterization, without ever touching the body of the catheter with your hands. The device also consists of an internal connector joined to the catheter and contained in an external connector. The drainage end of the device has an end to which a urine bag can be connected via a suitable connector.
The Coloplast Company, through its Micro-hole Zone Technology, aims to set a new standard for bladder emptying. In fact, the Luja device represents a new generation of clinically differentiated catheters that define a new standard of care, guaranteeing a strong impact and clinical benefit. Through the micro-holes, it is possible

Tab. I. Indications, contraindications and complications related to intermittent self-catheterization.

| | |
|---|---|
| Indications | • People with a neurological bladder (or neurogenic)<br>• People without neurological problems, but with urinary retention problems<br>The clinical conditions that most frequently lead to the need for this procedure are stroke, Parkinson's disease, multiple sclerosis, spinal trauma and spinal cord injury or tumours of the Central Nervous System (CNS) |
| Contraindications | • Uncontrolled incontinence<br>• Urethral trauma<br>• Frequent urinary tract infections |
| Complications related to intermittent self-catheterization | • Infections<br>• Urethral stenosis<br>• Bladder perforation<br>• Creation of a false pathway<br>• Alteration of urine exam |

Fig. 1. (a) Catheter with internal connector. (b) Enlargement of the flextip area and (c) the micro-holes of the catheter (Coloplast, 2021).




to ensure complete emptying of the bladder through a free flow, reducing the risk of urinary tract infection (UTI).
The main operating features of the device are listed below:

- reduced mucosal suction: the flow only stops when the bladder is completely emptied, removing uncertainty and minimizing microtrauma;
- just one position to completely empty the bladder, eliminating complex repositioning;
- flexible tip for a gentle insertion;
- triple Action Coating Technology for the protection of urethra;
- dry-sleeve for hygienic handling.

## Regolatory status of the technology

### Regolatory status of the technology

Table II shows the regolatory status of the technology.

### Technological alternatives

There are some technological alternatives to the use of intermittent bladder catheters: permanent urethral urinary catheters and suprapubic catheters. They differ mainly based on the mode of insertion and their use, as indicated in the Table III.

### Bladder catheter risks

Infection of the urinary tract is the greatest contraindication of bladder catheters. This risk is greater in the case of permanent catheters (both urethral and suprapubic) since, being kept in place for longer, they are more prone to bacterial contamination [2].
Further complications that can affect the urinary tract in the presence of a catheter are:

- bladder spasms;
- loss of urine (mild incontinence);
- accumulation of blood or debris inside the catheter;
- injury of the urethral canal;
- narrowing of the urethra;
- bladder stones;
- injuries to the bladder or rectum.

### EU Regulation 2017/745 and device risk class

Luja is an invasive device in relation to body orifices, non-implantable, non-surgical, classified as a Class I sterile device (without measuring function and intended for temporary use: the device is intended to be used for a continuous duration of less than 60 minutes – Rule 5 of EU Regulation 2017/745).
A CE mark is required for the marketing of this medical device in the European Union, certifying that the device meets all the regulatory requirements of the Medical Devices Directive.
Furthermore, under EU Regulation 2017/745 Luja can be classified as a Class I sterile device for which the involvement of a Notified Body is required for marketing within the European Union (MDCG 2019-15, 2019).
In fact, in the case of devices placed on the market in a sterile condition, an assessment of the manufacturing aspects of the device is required in order to ensure and

Tab. II. Regolatory status of the technology.

| | |
|---|---|
| **Technology** | Luja intermittent urinary catheter |
| **Manufacturer** | Coloplast S.p.A. |
| **CND classification** | U01010501 SONDE NELATON AUTOLUBRIFICANTI (NELATON SELF-LUBRICATING PROBES) |
| **Risk class** | Class I sterile (Is) |
| **CE Mark** | Yes |
| **Technology life-cycle phase** | Post-market |

Tab. III. Different types of urinary catheters [4].

| Technology | Permanent urethral urinary catheters | Suprapubic catheters |
|---|---|---|
| **Permanence or intermittence** | Permanent catheter, following insertion the catheter is left in place | Permanent catheter, following insertion the catheter is left in place |
| **Insertion mode** | The catheter is inserted into the bladder in the same way as the intermittent catheter and held in place by means of a water-filled balloon that prevents it from leaking. The opposite end has two openings: one allows urine to be excreted, the other one allows the balloon to be inflated. The urine is collected in a urine bag and its discharge can be regulated by means of a valve | The catheter is inserted into the bladder through a hole in the abdomen. The hole can be made through a surgical procedure under local or general anaesthesia. Urine is collected in a urine bag and its outflow can be regulated by means of a valve |
| **Utilisation** | The insertion of urethral catheters must be planned in the presence of a precise clinical indication | The suprapubic catheter is used when the urethra is damaged or obstructed, or when the person is unable to use an intermittent catheter |
| **Duration** | After insertion, the catheter can be kept in place for up to 2-3 months | After insertion it can be kept in place for up to 4-12 weeks |

maintain sterile conditions; the CE marking will be accompanied by the identification number of the reference of the Notified Body.
The post-market medical surveillance procedure (PMS) must be carried out. This report includes results and conclusions of the analysis of the data collected as part of the post-market surveillance and a description of any preventive and corrective actions taken. The report will be updated as necessary and made available to the competent authority upon request.
In addition, a Technical File (or Investigator's Dossier) must be provided containing detailed information on the medical device including the demonstration of conformity of the device as set out in EU Regulation 2017/745. It is also necessary to provide clinical data related to the device in question.
Finally, as with all devices, the Luja device must be audited annually by a Notified Body to ensure continued compliance. Failure to pass the audit will invalidate the CE marking certificate.

*Preclinical evaluation of the medical device*

The evaluation of pre-clinical testing procedures cannot disregard the results of the literature review and all validations, controls and tests performed. To plan, conduct and continuously document a clinical evaluation, manufacturers must:

a) establish and update a clinical evaluation plan that includes at least:
   - the identification of general safety and performance requirements to be supported by relevant clinical data;
   - a specification of the intended use of the device;
   - a clear definition of the target groups with clear indications and contraindications;
   - a detailed description of the expected clinical benefits for patients, including relevant outcome parameters;
   - a description of the methods to be used for the assessment of the qualitative and quantitative aspects of clinical safety, with clear reference to the determination of residual risks and side effects;
   - an indicative list of the parameters to be applied to determine the acceptability of the risk-benefit balance for the different indications and intended use of the device;
   - an indication of how issues relating to component risks and benefits are to be addressed.
b) identify available clinical data related to the device, its intended use and any gaps in clinical evidence through a systematic review of the scientific literature;
c) review all relevant clinical data and assess their suitability to establish the safety and performances of the device;
d) produce, through appropriately designed clinical investigations in accordance with the clinical development plan, new or additional clinical data necessary to address outstanding issues;
e) analyse all relevant clinical data to draw conclusions on the safety and clinical performance of the device, including its clinical benefits.

*Clinical investigations*

In order to carry out the clinical investigation enabling the device to be placed on the market, it is necessary to

comply with the provisions of the Circular of 25 May 2021 issued by the General Directorate of Medical Devices and Pharmaceutical Service.
Following the entry into force of the EU Regulation 2017/745, no clinical investigation can be initiated without the sending of appropriate communication to the Ministry of Health and without the conditions provided for the initiation of the investigation having been fulfilled, as subsequently specified by D.Lgs. of 5 August 2022, n. 137. Furthermore, through the decree of the Minister of Health of 6 August 2021, the administrative procedures of national relevance were established for the submission of the application for clinical investigation for devices not bearing the CE marking and for those bearing the CE marking referred to in Article 74, section 2, of the Regulation, providing that the documentation attached thereto must include the favourable opinion expressed by the competent ethics committee.
It should be emphasised that, for devices under investigation belonging to class I or for non-invasive devices belonging to classes IIa and IIb, applicants may start the clinical investigation 30 days after the date of validation of the application, unless the Ministry of Health notifies within this period that the application has been rejected for reasons of protection of public health, safety or the health of the subjects and users, provided that the competent ethics committee has issued a favourable opinion in relation to the clinical investigation.
In order to proceed with the application for authorisation of the clinical investigation to the competent authority residing in the Ministry of Health, the following documents must be attached (www.salute.gov.it):

- letter of application;
- clinical investigation application form, including an appendix listing the documents supporting the application:
  - clinical investigation: application form under Medical Device Regulation 2017/745;
  - supporting documentation for the clinical investigation application: appendix with documentation to be attached;
  - declaration in lieu of the affidavit of the sponsor;
  - declaration in lieu of the affidavit of the responsible for the manufacture;
  - power of attorney.
- investigator's Dossier, comprising the following annexes:
  - manufacturer's instructions;
  - label templates;
  - instructions for use;
  - list of general safety and performance requirements and applicable standards;
  - summary of risk, benefit and risk management analysis.
- Clinical Investigation Plan and Clinical Evaluation Plan;
- declaration signed by the person responsible for the manufacture of the device under investigation, specifying that the device in question complies with the general safety and performance requirements;
- copy of the opinion/single opinion issued by the Ethics Committee/Coordinating Ethics Committee depending on whether there are one or more trial centres in Italy;
- proof of insurance coverage or indemnification of subjects in case of damage;
- documents to be used to obtain informed consent, including the patient information form and the informed consent document in Italian language;
- description of the provisions aimed at ensuring compliance with the applicable rules on the protection and confidentiality of personal data;
- proof of payment of the fee of 2.245,20€;
- declaration in lieu of affidavit of the natural person acting as legal representative of the sponsor and of the person responsible for the manufacture;
- copy of the power of attorney, if any, to the person who submits the application, that is the receiver of communications from the Competent Authority;
- documentation on the suitability of the investigators' health facilities;
- list of trial centres and their ethics committees, including all their PEC addresses;
- other documents, where applicable (e.g. Opinion of the Expert Panel, CE Certificates of Notified Bodies, Decisions of other Competent Authorities, PMCF Plan, Enrolment Procedure Documentation and Publicity Material, opinions of other Ethics Committees).

In order to proceed with the submission of the clinical investigation application for the proposed medical device, it is necessary to draw up the Clinical Evaluation Plan or Clinical Investigation Plan (CIP), which describes in detail how the clinical study with the Luja device will be conducted. In particular, the CIP defines "the objective, design, methodology, statistical considerations and organisation of the study. The protocol also provides the background information and rationale for the clinical study" (Code of Good Clinical Practice for the Conduct of Clinical Trials of Medicinal Products, GCP).
The clinical investigation plan assumed with the Luja device can be found in Appendix 1, while in Appendix 2 it is possible to find a guide to filling in the "Clinical Investigation Application Form", including information on the hypothesised clinical protocol for the Luja device.

## References

[1] Di Santo S. Posizionamento di Catetere Vescicale. Aggiornato il 26.08.21. Available at: https://www.nurse24.it/studenti/procedure/posizionamento-di-catetere-vescicale.html (Accessed on: 30/10/2022).

[2] Medical Center. Catetere vescicale: che cos'è e cosa serve. Available at: https://www.e-medical.it/blog/catetere-vescicale-che-cose-e-cosa-serve (Accessed on: 30/10/2022).

[3] NHS. Trust Guideline for the Management of Teaching Clean Intermittent Self-catheterization, 2020. Available at: https://www.nnuh.nhs.uk/publication/download/teaching-of-clean-intermittent-self-catheterization-management-of-v4 (Accessed on: 30/10/2022).

[4] NHS. Types – urinary catheter. Available at: https://www.nhs.uk/conditions/urinary-catheters/types (Accessed on: 30/10/2022).

[5] Wellspect. Una guida rapida alle diverse tipologie di catetere. Available at: https://www.wellspect.it/vescica/il-cateterismo-intermittente/la-scelta-del-catetere/differenti-tipologie-di-catetere#:~:text=Cateteri%20intermittenti,dalla%20maggior%20parte%20delle%20persone (Accessed on: 30/10/2022).

[6] Vannini C. Autocateterismo intermittente – CIC. Aggiornato il 17.07.20. Available at: https://www.nurse24.it/dossier/incontinenza/procedura-autocateterismo-intermittente-uomo-donna.html (Accessed on: 30/10/2022).

Chapter 7

# Assessment phase

Coherent with the HTA approach, an expert advisory board was established with the aim of providing expertise for the integration of evidence coming from the existing literature.
The virtual meeting was held on December 2, 2022.

The following table shows the main feedback received from the experts (Tab. I).

Tab. I. Experts' opinion.

| | |
|---|---|
| General comments of expert panel | The following points were shared and appreciated by the panel of experts:<br>• the proposal to evaluate from different points of view the intermittent catheterization (IC) procedure, commonly used in people suffering from neurological and non-neurological pathologies, associated with complications and with an increased risk for patients of contracting urinary tract infections (UTIs)<br>• the need to answer the questions indicated and which have not yet been answered (e.g. which pathological conditions require intermittent catheterization and which of these are most associated with urinary tract infections, which type of catheter is most associated with UTIs, etc.), in particular "what are the real needs of patients who need intermittent catheterization"<br>• the "value based" approach of patient management with IC, in the various declinations of personal, allocative, technical and social value<br>• the project objective of identifying the main health needs of catheterized patients and action priorities for value-based management<br>• the applied methodology and the feasibility analysis which focused on the domains of the EUnetHTA core model HTA (CUR, ECO and TEC)<br><br>The experts stressed the importance of a multidisciplinary approach for the management of IC with the active involvement of both clinicians and nurses.<br>The experts underlined the heterogeneity and complexity of the various clinical conditions that may require catheterization as well as the variability of their clinical-epidemiological burden, especially in Italy.<br>The experts also underlined the importance of greater prevention of UTIs related to IC.<br>The importance of greater patient involvement was emphasized. In Italy, the actions of patient Associations but also of citizens are very strong.<br>With regard to the medical device under study, the potential characteristics and opportunities to enhance patient safety and improve their quality of life should be considered (as reported in: Cittadinanzattiva. Carta della qualità e della sicurezza delle cure per pazienti e operatori sanitari. 2020. Available at: https://www.cittadinanzattiva.it/multimedia/import/files/progetti/salute/CARTA_della_qualit%C3%A0_e_della_sicurezza_delle_cure_per_pazienti_e_operatori_sanitari_1.pdf). Experts have highlighted the need to:<br>• collect information directly from patients with IC and caregivers on the needs of these patients, differentiated from each other being a very heterogeneous population, in order to reduce the risk of complications and UTIs but also to improve the patients' quality of life<br>• produce an evaluation that includes the point of view of patients and caregivers on the IC procedure and on the most suitable devices to manage it<br>• provide patients with information on the IC and on the correct use of the device, with attention to the aspects of hygiene and infection prevention, accurately manage informed consent, taking into account the specificities of the person and the different context of life of the patient (hospital, home, nursing home, etc.) |
| Comments on review of the literature | According to the experts, the literature review was performed correctly from a methodological point of view and was fundamental to highlight the epidemiological gap on the number of patients with IC in Italy as well as on the prevalence of UTIs related to IC. This gap can be filled with further ad hoc studies aimed at producing scientific evidence on this health topic.<br>The epidemiological data on the UTIs burden are heterogeneous in relation to the target population studied, the size of the sample, the study design, the definition of UTIs and the basic disease considered.<br>Studies on the burden of IC-related UTIs in patients with multiple sclerosis and benign prostatic hyperplasia are still limited and more studies are needed to define the clinical-epidemiological burden. However, UTIs are also present in these target populations and underline a health need that must also be taken into account in these patients. |
| Comments on economic model | The members of the Advisory Board believe that the economic assessment presented is consistent. However, they underlined the need to build economic models that evaluate the cost-effectiveness of the different types of available catheters and that take into account the complications avoided (e.g. UTI), even with head-to-head comparisons.<br>Furthermore, it would be useful to build ad hoc models on specific target populations and specific diseases that require catheterization. |
| Final comments | All the experts expressed particular interest in the contents proposed during the meeting, underlining the importance of working and producing evidence in this area in a perspective of value-based healthcare. The problem of IC-related UTIs is a serious problem and, unfortunately, underestimated. It deserves to be evaluated, deepened and disclosed in order to identify real and, where possible, innovative solutions.<br>Finally, the panel expressed particular interest in the proposed study and the pre-assessment of the new technology under study, underlining the importance of the HTA evaluation of medical devices. |

# Application form under Medical Device Regulation 2017/745

## Application form - version 1.0

## Section 1: clinical investigation identification

### 1.1 SPONSOR IDENTIFICATION

| | |
|---|---|
| Name | [TO BE INSERTED] |
| Address | [TO BE INSERTED] |
| Telephone number | [TO BE INSERTED] |
| E-mail | [TO BE INSERTED] |

- **Contact person of the sponsor**

| | |
|---|---|
| First name | [TO BE INSERTED] |
| Last name | [TO BE INSERTED] |
| Telephone number | [TO BE INSERTED] |
| E-mail | [TO BE INSERTED] |

- **Sponsor's legal representative identification**

Do you have a legal representative? □ Yes □ No [TO BE INSERTED]
If yes, complete the information related to the legal representative (section 1.2)

### 1.2 LEGAL REPRESENTATIVE IDENTIFICATION

| | |
|---|---|
| Organisation name | [TO BE INSERTED] |
| Address | [TO BE INSERTED] |
| Telephone number | [TO BE INSERTED] |
| E-mail | [TO BE INSERTED] |

- **Contact person of the legal representative**

| | |
|---|---|
| First name | [TO BE INSERTED] |
| Last name | [TO BE INSERTED] |
| Telephone number | [TO BE INSERTED] |
| E-mail | [TO BE INSERTED] |

- **Contact person for the clinical investigation** [TO BE INSERTED]

□ Same as contact person of sponsor
□ Same as contact person of legal representative
□ Other
If you selected other, please fill in the section below related to the other contact person for this clinical investigation

- **Other contact person for the clinical investigation**

| | |
|---|---|
| First name | [TO BE INSERTED] |
| Last name | [TO BE INSERTED] |
| Address | [TO BE INSERTED] |

### 1.3 Clinical investigation type

Select the appropriate regulatory pathway for the application:
☒ Clinical investigation application (MDR Art. 62(1))
☐ PMCF investigation notification (MDR Art. 74(1))
☐ Other clinical investigation application/notification – national application (MDR Art. 82(1))

### 1.4 Submission type [TO BE INSERTED]

☐ First submission in the EEA
☐ First submission at the national level (clinical investigation has been already submitted in EEA)
In this case, please provide the clinical investigation ID (CIV-ID) provided

_____

☐Resubmission
Please provide the CIV-ID if already available

### 1.5 Participating countries within the EU/EEA/UK (Northern Ireland), Turkey and Switzerland

Select the participating countries for the clinical investigation [TO BE INSERTED]

### 1.6 Participating countries outside EU/EEA/UK

If this study is part of a multi-site clinical investigation outside the EU/EEA/UK, please provide a list of all the non EU/EEA countries the study plans to be carried out in.
[TO BE INSERTED]

### 1.7 Clinical Investigation Plan (CIP)

CIP Code [TO BE INSERTED]
CIP Version [TO BE INSERTED]
CIP Date [TO BE INSERTED]

### 1.8 Clinical investigation title

Full title: effectiveness of the Luja medical device in reducing the development of UTI related to the use of catheters by hospitalised patients.
Short title: effectiveness of the Luja medical device in reducing the development of UTI.
Title for lay people: effectiveness of the Luja medical device in reducing the development of Urinary Tract Infection (UTI) related to the use of catheters by hospitalised patients.

## Section 2: clinical investigation description

### 2.1 Scientific opinion

Has the manufacturer consulted with an expert panel as outlined in Art. 61(2) of Regulation (EU) 2017/745: ☐ Yes ☐ No [TO BE INSERTED]

### 2.2 Design of the clinical investigation

[TO BE INSERTED]
☐ Exploratory investigation
☐ Confirmatory investigation
☐ Observational investigation

[TO BE INSERTED]
☐ First in human investigation
☐ Not first in human

### 2.3 Design methodology

[TO BE INSERTED]
☐ Case Control ☐ Controlled ☐ Cross-sectional ☐ Doble blind
☐ Parallel ☐ Randomised ☐ Open ☐ Other

### 2.4 Fase di sviluppo

[TO BE INSERTED]
☐ Pilot stage ☐ Pivotal stage ☐ Post-market stage

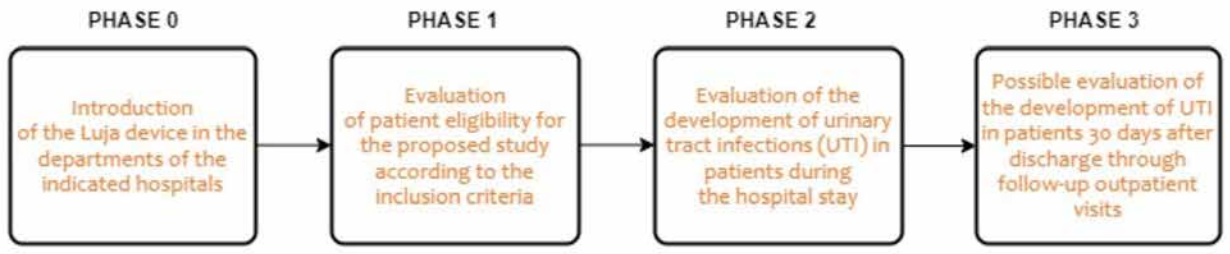
## 2.5 Objectives and endpoints

| | |
|---|---|
| Primary objective(s) | Verification of the efficacy of Luja device assessed in terms of side effects (adverse events) determined by the development of UTIs related to the use of catheters by patients admitted and selected for the proposed study |
| Secondary objective(s) | Healthcare costs incurred due to urinary tract infections that develop in in-patients e.g. in terms of prolonged length of stay, long-term disability, additional economic burden on healthcare systems, patients and their families, deaths for which infection is a contributing cause, absence from work and/or hospital/ambulatory visits |
| Other objective(s) | Not applicable |
| Primary endpoint(s) | Verification of the reduction in the adverse events caused by the development of UTIs in patients admitted and selected for the proposed study. The presence of infections is assessed in patients both during the hospitalisation period and 30 days after their discharge |
| Secondary endpoint(s) | Assessing both the healthcare costs incurred due to UTIs developing in in-patients and the cost of acquiring the device, taking into account the potential reduction in infections that the device can bring |
| Other endpoint(s) | Not applicable |

## 2.6 Synopsis of the clinical investigation

The clinical protocol can be divided into 3 phases, preceded by an initial phase (phase 0), which is the prerequisite for conducting the clinical study. The clinical protocol is shown in the figure below:

Fig. 4. Clinical protocol for the Luja device study.




- **Phase 0**: introduction of the Luja device in the departments of the indicated hospitals;
- **Phase 1**: evaluation of patient eligibility for the proposed study according to the inclusion criteria: adult patients (age > 18 years) admitted to the indicated department during the period of the study. A prerequisite is that they do not already have an infection (infection that is neither clinically manifest nor incubating at the time of hospital admission);
- **Phase 2**: evaluation of the development of urinary tract infections (UTI) in patients during the hospital stay. In-patients may only use the new intermittent urinary catheter during the hospitalisation period;
- **Phase 3**: possible evaluation of the development of UTI in patients 30 days after discharge through follow-up outpatient visits.

## 2.7 Planned number of subjects

In Europe [N1]
In Asia [N2]
In Africa [N3]
In North America [N4]
In South America [N5]
In Oceania [N6]
*Total planned number of subjects:* ***[$N_{total}$]***

## 2.8 Duration of clinical investigation

Estimated start date [TO BE INSERTED]
Estimated end date [TO BE INSERTED]

## 2.9 Population

### 2.9.1 Medical condition

Is there an associated medical condition? ☒ Yes ☐ No
Is the medical condition considered to be rare? ☐ Yes ☒ No

### 2.9.2 Therapeutic area

Select the therapeutic area that the clinical investigation falls under:

- **Target population**: Adult patients (age > 18 years) admitted to the indicated department during the period of the study;
- **The pathological conditions under analysis**: patients with spinal cord injury (SCI) and patients with neurogenic bladder, in particular neurogenic lower urinary tract dysfunction (NLUTD).

### 2.9.3 Gender of subjects

☐ Female ☒ Male ☐ Other

### 2.9.4 Inclusion criteria

Adult patients (age > 18 years) admitted to the indicated department during the period of the study, the pathological conditions under analysis are: patients with spinal cord injury (SCI) and patients with neurogenic bladder, in particular neurogenic lower urinary tract dysfunction (NLUTD).

### 2.9.5 Exclusion criteria

All patients who do not fit the inclusion criteria.

### 2.9.6 Type of subjects that the clinical investigation plans to recruit

☐ Healthy
☒ Patients
☒ Vulnerable population
☐ Incapacited subject
☐ Minors
☐ Pregnant women
☐ Breastfeeding women
☐ Patients in emercency situations
☐ Other (please specify)

### 2.9.7 Age range of the participants that the clinical investigation plans to include

☐ In utero
☐ Newborns (from0 to 27 days)
☐ Infants and toddlers (from28 days to 23 months)
☐ Children (from 2 to 5 years)
☐ Adolescents (from 12 to 17 years)
☒ Adults (from 18 to 84 years)
☒ Eiderly (from 85 years)

## 2.10 Scope of the investigational device

### 2.10.1 Combined investigation medical device/in vitro diagnostic?

☐ Yes ☒ No
If yes, please provide the related IVD performance study identification number:
Not applicable

### 2.10.2 Is the application submitted in parallel with an application for a clinical trial on medicinal products?

☐ Yes ☒ No
If yes, please provide the EU Clinical Trial Number:
Not applicable

### 2.11 Coordinating investigation

| | |
|---|---|
| First name | [TO BE INSERTED] |
| Last name | [TO BE INSERTED] |
| Address | [TO BE INSERTED] |
| Telephone number | [TO BE INSERTED] |
| E-mail | [TO BE INSERTED] |

## Section 3: investigational device(s)

### 3.1 Investigational medical device

#### 3.1.1 Device purposes

Urinary tract infections (UTI) occur when bacteria develop in the urethra and bladder. These infections are capable of causing serious complications if not treated promptly, e.g. kidney damage. As a result of the literature review carried out, the aim of introducing the Luja device is to focus on the self-catheterization modality, demonstrating that this modality, when compared with permanent catheterization, would appear to be associated with a lower incidence of complications and thus better long-term compliance, which is possible thanks to the innovative technology of which the device is made (Micro-hole Zone Technology). Luja represents a new generation of clinically differentiated catheters that define a new standard of care by guaranteeing a strong impact and clinical benefit. Through the micro-holes it is in fact possible to ensure complete emptying of the bladder through a free flow, reducing the risk of the occurrence of urinary tract infections (UTI).
In addition, the new device enables to:

- reduced mucosal aspiration: the flow stops only when the bladder is completely emptied, eliminating uncertainties and minimising micro-trauma;
- unique positioning: enables complete bladder emptying (eliminating complex repositioning);
- flexible tip allows for gentle insertion;
- triple-action coating technology to protect the urethra;
- dry sleeve for better hygienic conditions.

#### 3.1.2 Device type

☐ Implantable
☐ System
☐ Active device
☐ Non-medical purpose
☐ Measuring function
☒ Sterile
☐ Reusable surgical instrument
☐ Software
☐ Intended to administer or remove medicinal substance

#### 3.1.3 Invasiness

Is it an invasive medical device? ☒ Yes ☐ No

### 3.1.4 Device identifiers

| | |
|---|---|
| Generic denomination | Luja intermittent urinary catheter |
| Device trade name | Luja |
| Model | [TO BE INSERTED] |
| Device name | Luja |
| European Medical Device nomenclature | U01010501 SONDE NELATON AUTOLUBRIFICANTI (NELATON SELF-LUBRICATING PROBES) |
| Medical device classification | Class I sterile (Is) |
| Classification rule | Rule 5 of EU Regulation 2017/745 |
| Device description | Luja device is a male catheter intended for intermittent catheterization and intermittent dilatation of the urethra. The device is sterile, single-use, ready-to-use and consists of a hydrophilic coating. In particular, Luja is an invasive device in relation to body orifices, non-implantable, non-surgical, classified as a Class I sterile device (without measuring function and intended for temporary use: the device is intended to be used for a continuous duration of less than 60 minutes - Rule 5 of EU Regulation 2017/745) |
| Intended (clinical) purpose | The aim of introducing the Luja device is to focus on the self-catheterization modality, demonstrating that this modality, when compared with permanent catheterization, would appear to be associated with a lower incidence of complications and thus better long-term compliance, which is possible thanks to the innovative technology of which the device is made (Micro-hole Zone Technology). Luja represents a new generation of clinically differentiated catheters that define a new standard of care by guaranteeing a strong impact and clinical benefit. Through the micro-holes it is in fact possible to ensure complete emptying of the bladder through a free flow, reducing the risk of the occurrence of urinary tract infections (UTI) |

Does the device contain or incorporate medicinal substance(s)? ☐ Yes ☒ No
If yes, please provide the medicinal substance(s) name(s): Not applicable

The device incorporates, as an integral part, or it is manufactured using:
☐ Non-viable tissues of human origin or their derivatives with an ancillary action
☐ Non-viable cells of human origin or their derivatives with an ancillary action
☐ Non-viable tissues of animal origin or their derivatives with an ancillary action
☐ Non-viable cells of animal origin or their derivatives with an ancillary action
☐ Non-viable biological substance other than those referred to in the previous points
☒ None of these proposals/not applicable

Is the Investigational Device CE marked? ☐ Yes ☒ No

If yes, please provide the information in the box below. Not applicable

To what extent is the intended purpose of the device in the clinical investigation covered by the CE mark?
☐ CE marked device will be used outside the scope of its CE mark
☐ CE marked device will be used within the scope of its CE mark and no additional procedures are foreseen in the clinical investigation
☐ CE marked device will used within the scope of its CE mark, but additional procedures are foreseen in the clinical investigation

Are those additional procedures considered to be burdensome and/or invasive?
☐ Yes ☐ No
Please, comment why do you consider as such? Not applicable

Information related to the Notified body involved, if applicable:
Notified body number [TO BE INSERTED]
Notified body name [TO BE INSERTED]

### 3.2 Previous clinical investigation

Has this device been investigated in a clinical investigation within the EU previously?
☐ Yes ☒ No
If yes, please provide the relevant reference number(s) (such as SIN, CIV-ID, other reference(s)) of the previous clinical investigations Not applicable

### 3.3 Scientific opinion/view

Has the investigational/study device been subject to a national scientific view/opinion from an Expert Panel
☐ Yes ☐ No [TO BE INSERTED]

### 3.4 Manufacturer of the investigational device

Is the manufacturer the same as the sponsor? ☐ Yes ☐ No [TO BE INSERTED]
If no, please fill in the requested information in section 3.4.1 and 3.4.2.

#### 3.4.1 Manufacturer information

Organisation name [TO BE INSERTED]
Address [TO BE INSERTED]
Telephone number [TO BE INSERTED]
E-mail [TO BE INSERTED]

- **Contact person of the manufacturer**

First name [TO BE INSERTED]
Last name [TO BE INSERTED]
Telephone number [TO BE INSERTED]
E-mail [TO BE INSERTED]

#### 3.4.2 Authorised representative

Organisation name [TO BE INSERTED]
Address [TO BE INSERTED]
Telephone number [TO BE INSERTED]
E-mail [TO BE INSERTED]

- **Contact person of the authorised representative**

First name [TO BE INSERTED]
Last name [TO BE INSERTED]
Telephone number [TO BE INSERTED]
E-mail [TO BE INSERTED]
Additional devices could be added by using a duplicated section 3, in appendix to this application form

## Section 4: comparator

### 4.1 Applicability of section 4

Is there a comparator included in the clinical investigation? ☐ Sì ☒ No
If yes, the section from 4.2 needs to be completed.

### 4.2 Type of comparator Not applicable

☐ Therapy
☐ Placebo
☐ No treatment
☐ Medical device

#### 4.2.1 Medical device as comparator

Is the comparator medical device CE marked? ☐ Yes ☐ No Not applicable
If yes, will the CE marked comparator medical device be used in the clinical investigation within the scope of its CE mark? ☐ Yes ☐ No Not applicable

| | |
|---|---|
| Generic denomination | Not applicable |
| Device trade name | Not applicable |
| Device name | Not applicable |
| Model | Not applicable |
| European Medical Device Nomenclature | Not applicable |
| Medical Device Classification | Not applicable |
| Device description | Not applicable |
| Intended (clinical) purpose: | Not applicable |

Does the comparator device contain or incorporate medicinal substance(s)?
☐ Yes ☐ No Not applicable

If yes, please provide the medicinal substance(s) name(s): Not applicable
The comparator device incorporates, as an integral part, or it is manufactured using:
☐ Non-viable tissues of human origin or their derivatives with an ancillary action
☐ Non-viable cells of human origin or their derivatives with an ancillary action
☐ Non-viable tissues of animal origin or their derivatives with an ancillary action
☐ Non-viable cells of animal origin or their derivatives with an ancillary action
☐ Non-viable biological substance other than those referred to in the previous points
☐ None of these proposals/not applicable

Additonal comparators could be added by using a duplicated section 4, in appendix to this application form.

## Section 5: national information

### 5.1 Study site information

Please provide the list of sites taking part in the clinical investigation

| Name of institution | Site address | Investigator attached to this site | Contact information of investigators |
|---|---|---|---|
| [Insert name of institution 1] | [Insert site address 1] | [Insert investigation attached to the site 1] | [Insert contact information of investigators 1] |
| [Insert name of institution 2] | [Insert site address 2] | [Insert investigation attached to the site 2] | [Insert contact information of investigators 2] |

Additional sites could be added by using a duplicated section 5.1, in appendix to this application form

### 5.2 Ethics committee information

Select the applicable option: [TO BE INSERTED]
☐ Ethics committee opinion available
☐ Ethics committee opinion under review
☐ Ethics committee opinion is not mandatory before submission to the competent authority

If an ethics committee has to be selected by the sponsor before submission, please provide the ethics committee information's below:
Organisation name [TO BE INSERTED]
Address [TO BE INSERTED]
Telephone number [TO BE INSERTED]
E-mail [TO BE INSERTED]

### 5.3 Status of the clinical investigation

Is the sponsor considered as commercial according to national legislation? [TO BE INSERTED]
☐ Yes ☐ No

### 5.4 Expected number of subjects recruited within the Member State

How many subjects are expected to be recruited into the study in the Member State you are applying to?
[TO BE INSERTED]

*I hereby certify that the information and documentation submitted with this application/notification is correct in detail and all the information requested has been supplied. The investigated (medical) device complies with the applicable general safety and performance requirements, apart from those covered by the investigation and that every precaution has been taken to protect the health and safety of the patient and/or user.*
*I confirm that all the clinical investigations information collected for this application, has been done in compliance with the European data protection legislation (GDPR).*
Name [TO BE INSERTED]
Position [TO BE INSERTED]

SIGNATURE
[TO BE INSERTED]

## Appendix 2

# Clinical investigation plan (CIP)

The clinical investigation plan defines the rationale, objectives, design, methodology, monitoring, implementation, registration and method of analysis of the clinical investigation with respect to the proposed medical device, in accordance with the EU Regulation 2017/745 in Annex XV, Chapter II, and point 3.

The following Table shows the information set out in Annex XV of EU Regulation 2017/745.

**Tab. 3.** Clinical Investigation Plan (CIP) (EU Regulation 2017/745 in Annex XV, Chapter II, point 3)

| 1 | General aspects | |
|---|---|---|
| 1.1 | Unique identification number of the clinical investigation, as referred to in Article 70, section 1 | [TO BE INSERTED] |
| 1.2 | Identification of the sponsor - name, address and contact details of the sponsor and, where applicable, name, address and contact details of the sponsor's contact person or legal representative within the meaning of Article 62, section 2, established in EU | [TO BE INSERTED] |
| 1.3 | Information on the principal investigator at each investigation site, the coordinating investigator of an investigation, the coordinates of each investigation site and the emergency coordinates of the principal investigator at each site. The roles, the responsibilities and the qualifications of the various types of investigators are specified in the clinical investigation plan | [TO BE INSERTED] |
| 1.4 | A brief description of the method of financing the clinical investigation and a brief description of the contract between the sponsor and the site | [TO BE INSERTED] |

▶

Tab. 3. *continues*

| 1 | General aspects | |
|---|---|---|
| 1.5 | General summary of the clinical investigation, in an official language of the EU determined by the Member State concerned | Urinary tract infections (UTI) occur when bacteria develop in the urethra and bladder. These infections are capable of causing serious complications if not treated promptly, e.g. kidney damage. As a result of the literature review carried out, the aim of introducing the Luja device is to focus on the self-catheterization modality, demonstrating that this modality, when compared with permanent catheterization, would appear to be associated with a lower incidence of complications and thus better long-term compliance, which is possible thanks to the innovative technology of which the device is made (Micro-hole Zone Technology). Luja represents a new generation of clinically differentiated catheters that define a new standard of care by guaranteeing a strong impact and clinical benefit. Through the micro-holes it is in fact possible to ensure complete emptying of the bladder through a free flow, reducing the risk of the occurrence of urinary tract infections (UTI).<br>In addition, the new device enables to:<br>• Reduced mucosal aspiration - the flow stops only when the bladder is completely emptied, eliminating uncertainties and minimising micro-trauma<br>• Unique positioning: allows complete bladder emptying (eliminating complex repositioning)<br>• Flexible tip allows for gentle insertion<br>• Triple-action coating technology to protect the urethra<br>• Dry sleeve for better hygienic conditions<br>The possible technological alternatives that can be adopted are: 1. permanent urethral urinary catheters and 2. suprapubic catheters. In both cases, this is a permanent catheter, which after insertion is left in place for up to 2-3 months or 4-12 weeks, respectively. The major problem with the use of these catheters is precisely the increased likelihood of urinary tract infections (UTI).<br>**Clinical investigation with the medical device:** following the use of the Luja catheter in a hospital setting in the chosen department, an assessment of patient eligibility will be carried out according to the inclusion criteria: adult patients (age > 18 years) admitted to the indicated department during the study period. A prerequisite is that they are not already infected (infection neither in manifest clinical form nor in the incubation phase at the time of hospital admission). Subsequently, the development of urinary tract infections (UTI) during the hospital stay is assessed. If necessary, evaluation of the development of UTI in patients up to 30 days after discharge is carried out through outpatient follow-up visits.<br>**Aim of the clinical investigation**: through the study, it is intended to ascertain whether, through the use of the Luja medical device in a hospital setting, a reduction in the number of UTI infections occurring in patients admitted to the indicated department can be ascertained. In addition, the aim is to assess how much the introduction of the new technology will affect the costs of the National Health Service. According to the expected results, in fact, there will be a reduction in the healthcare costs incurred due to the development of infections occurring both in in-patients in terms of e.g. prolonged length of stay, long-term disability, additional economic burden for healthcare systems, patients and their families, deaths for which the infection is a contributory cause, absence from work and/or hospital/ambulatory visits. |
| 2 | **Identification and description of the device, including intended use, manufacturer, traceability, target population, materials that come into contact with the human body, medical or surgical procedures inherent to its use and the training and experience required for its use, review of reference literature, current state of the art of clinical care in the relevant field of application, and the proposed benefits of the new device** | **Device identification and description**: Luja device is a male catheter intended for intermittent catheterization and intermittent dilatation of the urethra. The device is sterile, single-use, ready-to-use and consists of a hydrophilic coating<br>**Manufacturer**: Coloplast S.p.A. (Via dei Trattati Comunitari Europei, 1957-2007, 9/F \| 40127 Bologna (BO) \| tel 051 4138 000 - https://www.coloplast.it/)<br>**Traceability: [TO BE INSERTED]**<br>**Target population**: adult patients (age > 18 years) admitted to the indicated department during the period of the study. The pathological conditions in analysis are: patients with spinal cord injury (SCI) and patients with neurogenic bladder, in particular neurogenic lower urinary tract dysfunction (NLUTD).<br>**Materials that come into contact with the human body**: the material in contact with patients is determined by the constituent material of the Luja device: A detailed description of the materials can be found in the "Product Composition Nautilus Male Doc. No. (VV-0307230)" not attached to the documentation examined.<br>**Medical or surgical procedures pertaining to its use and the training and experience required for its use**: the intermittent urinary bladder catheter is primarily intended for self-catheterization, the patient will need to be instructed on how to be able to insert the catheter themselves. It could also be used by health workers and personnel.<br>**Literature review**: as part of the feasibility study, several systematic literature reviews were carried out to assess the clinical epidemiological burden of complications related to intermittent catheterization in the adult population with spinal cord injury, multiple sclerosis and benign prostatic hypertrophy. The results obtained following the literature review (documentation provided by Coloplast S.p.A., PubMd, Web of Science) show that the most common complications related to catheterization are UTI. The key-words identified were: intermittent, catheterization, catheterization and complication.<br>**Current state of the art of clinical care in the relevant field of application and the advantages proposed by the new device**: intermittent catheterization is often indicated for self-catheterization; compared to assisted catheterization (by an operator or nurse), it appears to be associated with a lower incidence of complications and thus better long-term efficacy, which is possible thanks to the innovative technology of which the device is made (Micro-hole Zone Technology). Luja represents a new generation of clinically differentiated catheters that set a new standard of care by guaranteeing a strong clinical impact and benefit. Through the micro-holes it is indeed possible to ensure complete emptying of the bladder through a free flow, reducing the risk of the occurrence of urinary tract infections (UTI). |

Tab. 3. *continues*

| | | |
|---|---|---|
| 1 | General aspects | |
| 3 | Risks and clinical benefits of the device to be examined and the justification of the corresponding clinical results foreseen in the clinical investigation plan | There are no clinical risks in the use of the Luja medical device. Through this study, we want to investigate whether, through the use of the Luja medical device in healthcare, it is possible to attest to a reduction in the number of UTIs occurring by patients included in the clinical investigation. |
| 4 | Description of the relevance of clinical investigation within the state of the art of clinical practice | Studies previously conducted on the subject show that permanent catheterization is associated with a higher incidence of complications and thus lower long-term efficacy. The Luja medical device, through its new micro-hole technology, represents a new generation of clinically differentiated catheters that set a new standard of care by ensuring a high clinical impact and benefit. Through the micro-holes it is indeed possible to ensure complete emptying of the bladder through a free flow, reducing the relative risk of the occurrence of urinary tract infections (UTI). |
| 5 | Objectives and hypotheses of the clinical investigation | The aim of this study is to ascertain the effectiveness of the Luja medical device by assessing the side effects in terms of adverse events occurring in hospitalised patients that are related to the occurrence of UTIs. Through the study, the aim is to assess whether the use of the proposed device leads to a reduction in the incidence of patients contracting urinary tract infections and, at the same time, to estimate the reduction in costs resulting from the use of the Luja device in the treatment of infectious and inflammatory complications related to UTI. |
| 6 | Designing the clinical investigation and testing its soundness and scientific validity | |
| 6.1 | General information such as the type of investigation and criteria for the selection, endpoints and variables indicated in the clinical evaluation plan | **Type of survey:** [TO BE INSERTED]<br>**Selection criteria:** [TO BE INSERTED]<br>**Endpoint**: the aim of the clinical study is to assess the incidence of UTIs contraction by patients both during the in-patient period and in the period following their discharge (within 30 days after discharge) in order to determine whether it is reduced with the use of the proposed device.<br>**Variables**: two indicators to assess the rate of contraction of UTIs occurring both during the hospitalisation period and in the period following their discharge (within 30 days after discharge). |
| 6.2 | Information on the device being investigated, on any comparator products and on any other device or dressing to be used in the clinical investigation | Luja is an invasive device in relation to body orifices, non-implantable, non-surgical, classified as a Class I sterile device (without measuring function and intended for temporary use: the device is intended to be used for a continuous duration of less than 60 minutes - Rule 5 of EU Regulation 2017/745).<br>No comparison devices will be used during the conduct of the clinical investigation. However, the results obtained will be compared with data already in the literature about the incidence of UTI and the use of permanent catheters. |
| 6.3 | Information on the subjects, the selection criteria, the demographic size of the survey population, the representativeness of the survey population in relation to the target population and, if applicable, information on vulnerable participants, such as children, pregnant women, immunodeficient or elderly subjects | Subjects participating in the clinical study are adult patients (age > 18 years) admitted to the indicated department during the study period. The pathological conditions under analysis are: patients with spinal cord injury (SCI) and patients with neurogenic bladder, in particular neurogenic lower urinary tract dysfunction (NLUTD). |
| 6.4 | Details of measures to be taken to minimise systematic error and management of potential confounding factors | [TO BE INSERTED] |
| 6.5 | Description of clinical procedures and diagnostic methods relevant to the clinical investigation, indicating in particular any deviation from normal clinical practice | Following the use of the Luja catheter in a hospital setting in the chosen department, an assessment of patient eligibility will be carried out according to the inclusion criteria: adult patients (age > 18 years) admitted to the indicated department during the study period. A prerequisite is that they are not already infected (infection neither in manifest clinical form nor in the incubation phase at the time of hospital admission).<br>Next, the development of urinary tract infections (UTI) during the hospital stay is assessed. If necessary, evaluation of the development of UTI in patients up to 30 days after discharge is carried out through outpatient follow-up visits. |
| 6.6 | Monitoring plan | Following the eligibility assessment of in-patients, their health status will be monitored both during the period of admission and in the 30 days following discharge, in order to ascertain whether patients have contracted UTI related to the use of the Luja intermittent catheter. Through the proposed device, it is intended to prove the presence of a lower risk of contracting the infection. |
| 7 | Statistical considerations, and their justification, including a power calculation for the sample size, if applicable | [TO BE INSERTED] |
| 8 | Data management | [TO BE INSERTED] |
| 9 | Information on possible changes to the clinical investigation plan | Not applicable |

Tab. 3. *continues*

| | | |
|---|---|---|
| 1 | General aspects | |
| 10 | Policy on follow-up and management of any deviations from the clinical investigation plan at the investigation site and clear prohibition of applying deviations from the clinical investigation plan | Not applicable |
| 11 | Responsibility for the device, in particular control of access to the device, comments concerning the device used in the clinical investigation and return of unused resources, expired or faulty devices | The clinical protocol can only be initiated following inpatient use of the Luja device in the indicated department of the hospital in which the proposed study will take place. Luja is a non-implantable, sterile, body orifice invasive device for which unused resources and/or expired or failed devices used during the clinical investigation will be returned. |
| 12 | Declaration of compliance with recognised ethical principles for medical research involving human subjects and with the principles of good clinical practice regarding clinical investigation of devices, as well as with all applicable regulatory requirements | [TO BE INSERTED] |
| 13 | Description of informed consent | [TO BE INSERTED] |
| 14 | Safety reports, including definitions of adverse events and serious adverse events, device defects, procedures and deadlines for submission of such reports | [TO BE INSERTED] |
| 15 | Criteria and procedures for the follow-up of subjects following the termination, temporary discontinuation or early termination of an investigation and for the follow-up of subjects who have withdrawn their consent and procedures for cases of abandonment by subjects. For implantable devices, these procedures cover at a minimum traceability | For the conduct of the study, it is necessary to assess the clinical status of patients admitted to the departments of the indicated hospitals regarding the occurrence of UTI.<br>An early termination of the clinical investigation is not foreseen; in the event of dropouts, only the indicator concerning the rate of contraction of UTI during the hospitalisation period will be taken into account. |
| 16 | A description of how care will be provided to subjects at the end of their participation in the clinical investigation, if additional care is required as a result of participation in that investigation and such care differs from that normally provided for the clinical condition in question | No additional treatment is required after the end of participation in the clinical investigation. |
| 17 | Policy on the establishment of the clinical investigation report and publication of the results in accordance with the legal requirements and ethical principles set out in Chapter I, point 1 | The definition of a clinical investigation and the publication of the results shall be carried out in accordance with EU Regulation 2017/745, Annex XV, Chapter 1, point 1: "Ethical Principles - Each step of the clinical investigation, from the initial consideration of the necessity and justification for the study to the publication of the results, shall be carried out in accordance with recognised ethical principles". |
| 18 | List of technical and functional characteristics of the device, with specific indication of those that are the subject of the survey | The Luja device is a male catheter intended for intermittent catheterization and intermittent dilatation of the urethra. The device is sterile, single-use, ready-to-use and consists of a hydrophilic coating (Coloplast, 2021). In particular, it represents a new generation of clinically differentiated catheters that set a new standard of care by guaranteeing a high clinical impact and benefit. Through the microholes, it is indeed possible to ensure complete emptying of the bladder through a free flow, reducing the risk of urinary tract infection (UTI).<br>In addition, the new device enables<br>• reduced mucosal aspiration: the flow stops only when the bladder is completely emptied, eliminating uncertainties and minimising micro-trauma<br>• unique positioning: enables complete bladder emptying (eliminating complex repositioning)<br>• flexible tip: allows for gentle insertion<br>• triple-action coating technology to protect the urethra<br>• dry sleeve for better hygienic conditions |