# Is urethral catheterization as urine collection method in young children feasible in general practice? A proof of concept study.

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# ABSTRACT

**Introduction:** The diagnosis of urinary tract infections in non-toilet trained children is challenging, partly because of the nonspecific presentation at young age and partly because it is not easy to obtain a reliable urine sample in this population. Moreover, a timely and correct diagnosis with a rapid start-up of targeted antibiotics is necessary to prevent kidney damage and systemic infections. In a low prevalence setting such as a general practice it is especially important to exclude urinary tract infections, therefore there is a need for a reliable urine collection method with low contamination rates.

**Literature review:** There is a wide variety of urine collection methods, which can be divided into non-invasive and invasive techniques. Especially in acutely ill children, most guidelines prefer urethral catheterization given the low contamination rates. The most reliable non-invasive method is the clean-catch method, which has contamination rates similar to urethral catheterization and is therefore recommended as first choice in some guidelines.

**Aim of the study:** Time-efficiency is very important in family medicine. Since non-invasive methods are often more time-consuming and there is still insufficient evidence around stimulation techniques, we will investigate if urethral catheterization as a urine collection method in non-toilet trained children is feasible in general practice.

**Methods:** We performed an interventional study combined with a nested interview study in 10 general practitioners from 4 different group practices across Flanders. Between 1st October 2024 and 28th February 2025 the general practitioners included non-toilet trained children presenting with fever, in whom a urine sample was deemed necessary. If a clean-catch attempt was unsuccessful, they proceeded to urethral catheterization. The primary outcome was success rate, secondary outcomes were time-efficiency and contamination rate. The opinions of the general practitioners and their experience were evaluated by questionnaires and an interview.

**Results:** At study start, all general practitioners assumed they were able of performing urethral catheterization and concluded it to be a promising technique. Nevertheless, only one child was included in the study. One general practitioner performed urethral catheterization successfully on the same child during two different episodes of illness. Both samples were not contaminated and there was a marked learning curve resulting in an important gain of time on the second catheterization. At the end of the study, general practitioners mentioned the low prevalence as the main barrier for catheterization.

**Conclusion:** Urethral catheterization was only performed twice by one general practitioner. The remaining general practitioners gave the low prevalence as main reason for not applying this technique in the future. This threshold should be interpreted in the context of underdiagnosis of urinary tract infections in children. In the future, there is a need to innovate and optimize non-invasive methods such as the clean-catch. In addition, more research is necessary on the appropriate indications for a urine sample in general practice in order to efficiently exclude urinary tract infections.

# NEDERLANDSTALIG ABSTRACT

**Introductie:** De diagnose van urineweginfecties bij niet-zindelijke kinderen is uitdagend, enerzijds door de aspecifieke presentatie op deze leeftijd en anderzijds doordat het bekomen van een betrouwbaar urinestaal in deze populatie niet evident is. Bovendien is een tijdige en correcte diagnose met een snelle opstart van gerichte antibiotica noodzakelijk om nier schade en systemische infecties te voorkomen. In een lage prevalentie setting zoals een huisartsenpraktijk is het voornamelijk van belang om urineweginfecties uit te sluiten, daarom is er nood aan een betrouwbare urine opvangmethode met een lage contaminatiegraad.

**Literatuuronderzoek:** Er bestaat een grote verscheidenheid aan urine opvangmethoden, onder te verdelen in niet-invasieve en invasieve technieken. Zeker bij acuut zieke kinderen verkiezen de meeste richtlijnen urethrale katheterisatie gezien de lage graad van contaminatie. De meest betrouwbare niet-invasieve methode is de clean-catch methode, deze heeft een contaminatiegraad vergelijkbaar met urethrale katheterisatie en wordt daarom in enkele richtlijnen aangeraden als eerste keuze.

**Doel van de studie:** Tijds-efficiëntie is erg belangrijk in huisartsgeneeskunde. Aangezien de niet-invasieve methoden vaak meer tijdsintensief zijn en er nog onvoldoende evidentie is rond stimulatietechnieken, zullen we in deze studie nagaan of er een plaats is voor urethrale katheterisatie bij niet-zindelijke kinderen in de huisartsenpraktijk.

**Methode**: Het betrof een interventionele studie, gecombineerd met een interview studie bij 10 huisartsen uit 4 verschillende groepspraktijken verdeeld over Vlaanderen. Van 1 oktober 2024 tot 28 februari 2025 includeerden de huisartsen niet-zindelijke kinderen met koorts zonder focus waarbij een urinestaal nodig was. Indien een poging tot clean-catch onsuccesvol was, gingen ze over tot urethrale katheterisatie. De primaire uitkomstmaat was de graad van succes, daarnaast werd er ook gekeken naar tijdsefficiëntie en de graad van contaminatie. De ervaring en meningen van de huisartsen werden geëvalueerd aan de hand van vragenlijsten en een interview.

**Resultaten**: Alle huisartsen gaven voor de start van de studie aan in staat te zijn te sonderen en zagen dit als een veelbelovende techniek. Desalniettemin werd er slechts één kindje in de studie geïncludeerd. Er werd bij hetzelfde kind tijdens twee verschillende ziekte-episodes een succesvolle urethrale katheterisatie uitgevoerd door dezelfde huisarts, beide stalen waren niet gecontamineerd en er was een aanzienlijke leercurve resulterend in een belangrijke tijdswinst bij de tweede katheterisatie. Bij afloop van de studie vernoemden huisartsen voornamelijk de lage prevalentie als drempel om katheterisatie toe te passen.

**Conclusie:** Urinaire katheterisatie werd slechts twee keer toegepast door één huisarts. De overige huisartsen gaven een te lage prevalentie als reden om de techniek niet toe te passen in de toekomst. Deze drempel moet worden geïnterpreteerd in de context van onder-diagnose van urineweginfecties bij kinderen. In de toekomst is er nood aan vernieuwing en optimalisatie van de niet-invasieve methoden zoals de clean-catch en moet er ook verder gekeken worden naar de juiste indicaties voor een urinestaal in de huisartsenpraktijk zodat we urineweginfecties efficiënt kunnen uitsluiten.

# TABLE OF CONTENTS

ABSTRACT....3
Nederlandstalig ABSTRACT....4
INTRODUCTION....7
LITERATURE REVIEW – a variety of urine collection methods....8
Methods....8
Results....8
Guidelines....10
Discussion....11
METHODS....13
Study design and registration....13
Eligibility criteria....13
Intervention....14
Adverse event reporting....14
Statistics and analysis....15
RESULTS....16
Characteristics of the included general practitioners....16
Patient characteristics....16
Urine collection results....16
Questionnaire at the start of the study....17
Questionnaire at the end of the study....18
Interviews at the end of the study....19
DISCUSSION....20
Prevalence of UTI in general practice....20
Urethral catheterization education and training....21
Urethral catheterization in boys compared to girls....21
Time-efficiency....21
Material and costs....22
Parental perception....22
Limitations and other contributing factors to our small sample size....23
CONCLUSION....24
FUNDING....24
BIBLIOGRAPHY....25
Appendix....27
Appendix 1 – Search string....27
Appendix 2 – Ethical approval....28

Appendix 3 – Questionnaires and interview ..... 29
Appendix 3.1 – Questionnaire PRE ..... 29
Appendix 3.2 – Questionnaire POST ..... 29
Appendix 3.3 – Interview at the end of the study ..... 30
Appendix 4 – Step-by-step instruction on urethral catheterization ..... 31
Appendix 5 – Recruitment of participants ..... 32
Appendix 7 – Clinical research protocol 30 August 2024 version 3.2 ..... 34

# INTRODUCTION

Urinary tract infections (UTI), comprising cystitis and pyelonephritis, are a common diagnosis in young children. The overall prevalence of UTI in children with unexplained fever is 7% (1) of which, 6% are diagnosed with cystitis and 0,6% pyelonephritis (2). However, the incidence of UTI in children varies with age, with a higher prevalence of UTI in non-toilet trained children (3). Regardless of sex, age < 3 months was a risk factor for UTI (4). The highest baseline prevalence rates were seen in uncircumcised boys less than 3 months old and females less than 12 months of age (5). In addition, prepubertal girls are three times more likely to have a UTI than boys (3,6).

An accurate and timely diagnosis is very important, because when these UTI remain undetected, they can cause several complications, for example renal scarring, renal failure or systemic infections (2). Because most acutely ill children present to primary care, general practitioners play a key role in preventing treatment delay and associated complications through early detection of UTI. However, the diagnosis of UTI in children who are not yet toilet trained is challenging. On the one hand because of the non-specific presentation at this young age and on the other hand because it is difficult to obtain a reliable urine sample in pre-continent children (1,2).

Symptoms of UTI vary with age and are less specific in infants, for example fever, failure to thrive, lethargy, vomiting, jaundice, irritability and hypothermia. In young children fever can be the only symptom of UTI (6,7). In older children more specific UTI symptoms such as dysuria, urgency, frequency, incontinence, malodorous urine, suprapubic pain, hematuria, fever and flank pain may be present (7). This age-related symptomatology contributes to the challenge of diagnosing UTI in infants.

Because of this non-specific presentation, physicians in primary care need appropriate urine collection methods to obtain a reliable urine sample (2). By a reliable urine sample, we mean a sample that is either able to identify the correct pathogen or to exclude UTI. Especially in low prevalence settings as primary care ruling out UTI is important. Fecal bacteria colonize the perineal area and distal urethra, resulting in contamination during urine collection in non-toilet trained children (especially in uncircumcised boys) and therefore making the diagnosis of UTI even more complicated (8). For this reason urine collection methods associated with low contamination rates are essential.

This study explores the implementation of a more reliable urine collection method in primary care. Therefore we started with a literature review of the existing urine collection methods and their quality, which were described in more detail in de following chapter.

# LITERATURE REVIEW – a variety of urine collection methods

## METHODS

On the 16th of March 2023 a first literature search was performed using the PubMed database. The search strategy was based on four main components including urine specimen collection, non-toilet trained children, diagnosis and urinary tract infections. A more detailed version of the search string can be found in Appendix 1. Articles were eligible for inclusion if each of these components were represented. First, we included systematic reviews, guidelines and randomized controlled trials. For more detailed information, we later added relevant original research studies by manual reference tracking of the systematic reviews. Other inclusion criteria were age (children < 16 years old), publication language (English) and availability of the full text. There were no limitations in terms of publication dates. An update of the search was performed on 1st December 2024. In addition relevant guidelines such as NHG-guidelines (Nederlands Huisartsen Genootschap) and NICE guidelines were consulted.

## RESULTS

202 articles were identified with the literature search of which 19 were relevant to the research question. Several invasive and non-invasive urine collection methods exist, presented in Figure 1. Invasive methods such as suprapubic aspiration (SPA) and urinary catheterization (UC) are sterile techniques associated with lower contamination rates (2,6,9,10). Contamination rates of UC ranged from 0% up to 9%, SPA had a contamination rate of 0,03% (2).

The most sensitive urine collection method for obtaining a urine sample is SPA, ultrasound guidance can increase the success rate of this method by assessing bladder filling (6,7). A disadvantage of SPA is that it is a painful procedure, therefore UC is a more acceptable invasive method, in addition UC has the highest success rate in collecting urine samples (6,7). When obtaining a urine sample by using UC, contamination rates were lower if the late-stream urine was cultured compared to the first-stream urine (respectively 0-2% and 5-7%) (2).

In primary care most physicians prefer non-invasive methods, because they are more feasible and seem more acceptable (1,2). One of the most used non-invasive techniques in primary care are urine bags, these are self-adhesive bags that can be applied to the genitalia after disinfection to reduce contamination (2). An adapted version of the adhesive bag was called ‘a midstream collector’ which has two compartments to separate the first-stream urine from the end-stream with the latter going immediately into the test tube (11). A second non-invasive technique are nappy pads, which are inserted in a clean diaper. When the child has urinated the pad can be removed and the urine will be extracted in a sterile container (2,12). These low-threshold techniques are associated with high contamination rates, ranging from 30% to 80% for adhesive bags, 64% for nappy pads and 10% for ‘the midstream collector’ (2,6,10–12). A recent randomized controlled trail (RCT) investigating the impact of the patients position while collecting a

urine sample by using bags, found there was no significant effect on the contamination rates (13).

A third non-invasive collection method is called clean-catch urine sampling. For this technique the child needs to urinate spontaneously, then the first-stream urine will directly be collected in a sterile container (2). The systematic review of Boon et al. (2021) investigated the diagnostic test accuracy of the different urine collection methods in outpatient children (2). Boon et al. (2021) concluded that among the various non-invasive methods, a clean-catch urine collection is the most reliable method. This technique has a contamination rate of 5% which is comparable to UC (2). Therefore a clean-catch urine sample can be a good and low-threshold alternative for UC in general practice.

In reality non-invasive techniques are time-consuming and messy (2,6). Comparing nappy pads and urine collection bags, the average time to obtain a urine sample by using a bag was 70 minutes and the average urine collection time by using nappy pads was 93 minutes (14). The clean-catch method had a median collection time of 30,5 minutes, with an interquartile range of 11 up to 66 minutes (15,16). Besides, it is difficult to catch a sample during a voiding event, when determining successfulness of the clean-catch method, 16% of the attempts resulted in a missed catch (15).

Because the urine collection time of these low-threshold non-invasive techniques is longer than UC and SPA, recent studies tried to enhance the clean-catch method by using voiding stimulation techniques (7). The systematic review of Chandy et al. (2020) evaluated the evidence of the effectiveness of non-invasive bladder stimulation techniques in pre-continent children compared with standard urine collection methods (16). Conclusions on these different techniques were summarized in the following paragraphs.

The most investigated technique to shorten the mean time to obtain a clean-catch urine sample is by bladder tapping and lumbar paravertebral massage (17). Chandy et al. (2020) included 6 preliminary studies and 1 RCT on this stimulation technique (16). This standardized clean-catch technique, described by Herreros et al. (2013) consists of three main steps. First, oral intake is stimulated based on the age and weight of the child, then a genital cleaning protocol follows and finally voiding is stimulated by suprapubic and lumbosacral percussion (17). A cross-sectional study demonstrated that diagnostic accuracy of urine samples using this technique was good (sensitivity 97%, specificity 89%) with low contamination rates, 5% in the bladder stimulation group and 8% in the UC group (18). Comparing all the evidence on this technique, the systematic review concluded it to be an effective stimulation technique, but level of evidence was low (16,18,19).

A second promising stimulation technique is called the “Quick-Wee method”. This most recent bladder stimulation technique uses a cold, saline-soaked gauze to stimulate urine voiding. Chandy et al. (2020) concluded this method showed some success in stimulating voiding and Boon et al. (2021) described the Quick-Wee method as relevant in primary care (2,16). Both conclusions were based on the same RCT comparing the Quick-Wee method to the standard clean-catch technique (20). The Quick-Wee method resulted in a more successful urine collection within 5 minutes, but even then it only worked in a

minority of patients (30%) (2,20). However, a more recent RCT showed conflicting findings on this simple and inexpensive intervention (21). This replication study of Branagan et al. (2022) did not observe a statistically significant increase in the collected urine samples using the Quick-Wee method in non-toilet trained children (21). The Quick-Wee method had a greater satisfaction among both parents and clinicians (2,20,21). Using this method parents can have a more active role in urine collection, which contributed to the high parent satisfaction rating (21). However, studies describing diagnostic accuracy of this method in the outpatient setting were not yet performed (2).

The most recent RCT on decreasing time to collect a clean-catch sample, investigated the use of point-of-care ultrasound (POCUS) in non-toilet trained children to assess bladder volume and stimulate urine voiding (22). There was a significant reduction in mean time to obtain a urine sample compared to the standard clean-catch (22). Another RCT investigated the impact of using POCUS prior to stimulated clean-catch urine collection, they found no significant improvement of success rate (23). In addition POCUS is not relevant for GPs, because an ultrasound is expensive and not yet part of the standard equipment in a family practice.

The systematic review concluded that there is a positive effect of stimulation techniques, but no conclusive recommendations can be made because of the heterogeneity of techniques and lack of replication in RCT's. Further research is necessary, focusing on the comparison of non-invasive stimulation methods, contamination rates, time-efficiency, feasibility, adverse events, parent and caregiver acceptability (16).

## GUIDELINES

There are different guidelines on the diagnosis and management of UTI in young children. Most European, American and Asian guidelines prefer invasive urine collection methods because of the low contamination rates (6–8,10). This is even more important in acutely ill children needing a rapid start-up of antibiotics. Therefore non-invasive techniques such as nappy pads and adhesive bags are not recommended in the guidelines because of the high contamination rates associated with the risk of misdiagnosing UTI (6,10,12).

Contrary to the European and American guidelines, the NICE guidelines recommend a clean-catch as the preferrable urine collection method (24). Updated guidelines from the Indian Society of Pediatric Nephrology (ISPN) prefer a clean-catch as initial attempt in stable non-toilet trained children and if unsuccessful, UC or SPA will be performed. Although the American Academy of Pediatrics (AAP) prefers UC or SPA in children between 2 and 24 months old, it suggests that invasive techniques can be avoided in stable children when a clean-catch sample tests negative for both nitrites and leucocytes (10,16). In acutely ill non-toilet trained children UC or SPA remains the preferred method (7).

The Dutch NHG-guidelines (Nederlands Huisartsen Genootschap), last updated in 2020, are in line with the NICE guidelines (24,25). In non-toilet trained children a clean-catch is the preferred method and if unsuccessful UC (performed by a pediatrician) is indicated (25). Before obtaining a clean-catch, it is recommended to clean the genitalia to reduce the risk of contamination. Urine samples obtained by using a urine bag are only suitable

to exclude UTI. To improve the chance of collecting a clean-catch, NHG guidelines also recommend the Quick-Wee method or the stimulation technique by performing bladder tapping and lumbar paravertebral massage (25).

## DISCUSSION

This literature search demonstrated that there are several invasive and non-invasive urine collection methods. Most guidelines prefer invasive techniques in non-toilet trained children, especially in those who need a rapid start-up of antibiotics. The clean-catch method is the most reliable non-invasive method with contamination rates comparable to UC. Therefore some guidelines recommend a clean-catch as initially attempt in stable children, because it is a successful method for ruling out UTI. Studies on stimulation techniques to improve success rate of the clean-catch method show variable results and level of evidence is low. Because there are few convenient, low threshold urine collection methods and data on diagnostic accuracy of these techniques is limited, early diagnosis of UTI in the outpatient setting remains challenging (2).

Besides the variation in recommendations by different national health organizations and guidelines. There also exist a significant practice variation in urine collection methods for non-toilet trained children within and between countries (26).

Several factors contribute to the choice of the used method. On the one hand, there are guidelines which prefer invasive methods with low contamination rates or when feasible, a clean-catch. On the other hand, choice is also determined by feasibility, the time available to obtain a urine sample, parent satisfaction, practical experience of the healthcare provider and severity of illness in pre-continent children at presentation.

In family medicine, time-efficiency is important. Because the urine collection time of non-invasive techniques is longer than invasive methods and there is not yet enough evidence on bladder stimulating techniques (such as the Quick-Wee method), this study investigated whether UC is feasible in general practice for the diagnosis of UTI in non-toilet trained children, in which it is not possible to obtain a clean-catch spontaneously.

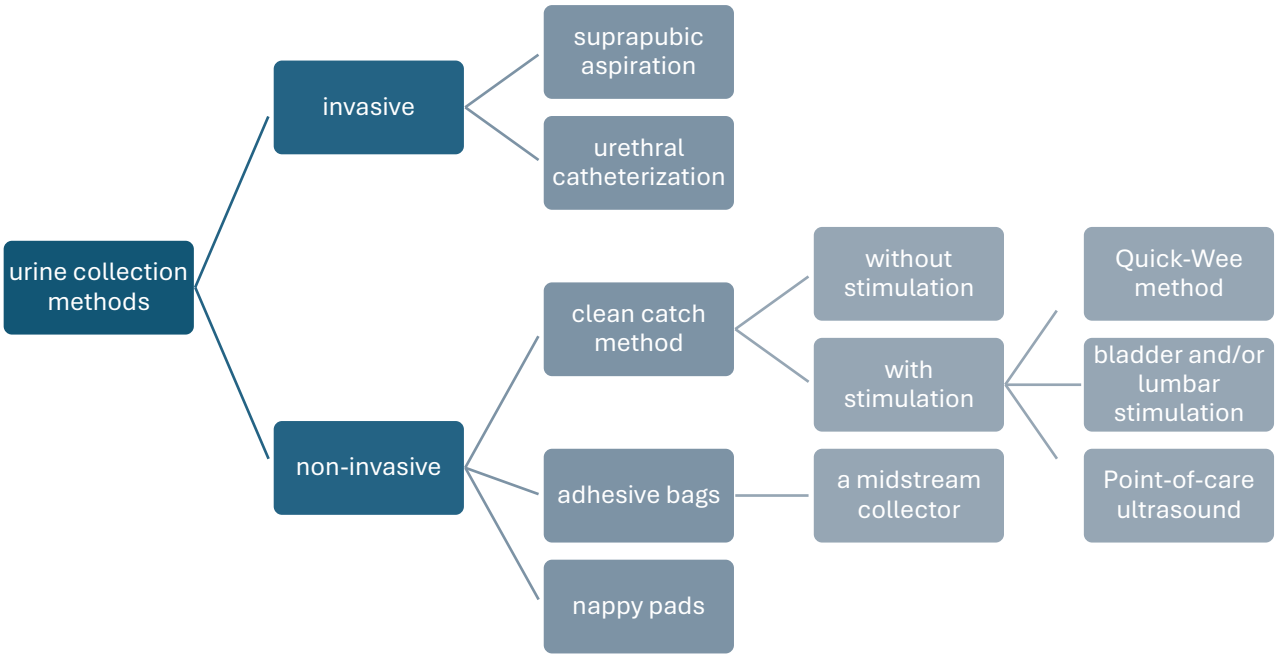


**Figure 1.** Overview of the existing urine collection methods.

# METHODS

## STUDY DESIGN AND REGISTRATION

Prior to the start of the study, the protocol was approved by the Clinical Trial Center UZ Leuven (S68066) and Ethics Committee Research UZ/KU Leuven (registration number B3222024001440). Approval was given on August 30, 2024 (Appendix 2).

We performed an interventional study combined with a nested interview study between 1st October 2024 and 28th February 2025 in four different family doctor practices across Flanders. Participating sites were Huisartsenpraktijk De Ceder (Schilde), Huisartsenpraktijk Den Els (Oelegem), Huisartsenpraktijk Linden (Linden) and Huisartsenpraktijk De Akkerhoorn (Zedelgem). All these practices have read the protocol and signed a clinical trial agreement.

The interventional part of the study focused on the feasibility of UC in general practice for diagnosing UTI in pre-continent children. This was done by observing success rate as primary outcome of the study. Secondary outcomes of the interventional part of the study were contamination rates and time-efficiency.

The interview study provided an insight in the general practitioner's thoughts on UC in general practice. Participating GPs were asked to fill in a questionnaire before and after the study (Appendix 3.1 and Appendix 3.2). The questionnaire at the end of the study was accompanied by a short one-on-one interview containing 2 additional questions (Appendix 3.3).

## ELIGIBILITY CRITERIA

We included 10 GPs from the participating sites mentioned above, inclusion criteria were as follows: (1) GP or GP in training, (2) working solo or in a group practice, (3) GP practice located in Flanders, (4) having regular consultations with children.

GPs approached pre-continent children presenting to ambulatory care in whom a urine sample was deemed necessary, for possible participation. Inclusion criteria were (1) pre-continent children) aged 3 months to 2 years, (3) presenting with a fever without an initial focus found during history and clinical examination and (4) parent or guardian was willing and able to give informed consent for participation. Exclusion criteria were as follows: (1) children who are continent, (2) children who are clinically unstable or where ambulatory care is not possible because of the poor overall clinical condition, (3) presence of contra-indications for UC (known urethral trauma, acute pelvic fracture), (4) recent genitourinary surgery, (5) genital malformations (e.g. hypospadias) and (6) antibiotics taken in the previous 7 days.

## INTERVENTION

When informed consent was obtained, the GPs recorded demographic information and clinical features of the child (sex, age, ethnicity, medical history, medications, symptoms and findings during clinical examination). Urinary catheterization was only attempted in those children for whom a clean-catch method was not successful. The urine sample was subsequently sent to the laboratory for urine culture and sediment, which is the reference standard. Following urine sample that was taken, participating GPs recorded the collection method (clean-catch or UC), whether it was successful, any problems encountered, the time it had taken, the perception of the parents, the laboratory results and the treatment. Treatment and other management decisions were left to the treating physicians' discretion.

At the start of the study, all participating GPs attended a training session on how to perform UC according to the guidelines. Training sessions consisted of a theoretical and practical part where the GPs were able to learn more about the study, the materials and could practice the procedure. The training session was supported by video material and every GP received a step-by-step plan on how to perform UC (Appendix 4), besides an overview of the materials and different steps, there was a link to an instruction video as well.

Each GP received 5 UC kits including all the materials needed for UC, more specifically a hydrophilic coated urinary catheter (SpeediCath® Child Charriere 6, length 20cm), a sterile urine container, a chlorhexidine based antiseptic (Hibidil®) and a set containing sterile gloves, sterile lubricant gel, sterile field, sterile tweezers and gauze swabs.

## ADVERSE EVENT REPORTING

The Ethics Committee Research UZ/KU Leuven and the Clinical Trial Center UZ Leuven requested for an adverse event reporting because they considered our study to be highly interventional, despite UC being a well-known intervention recommended in the guidelines. Adverse events were evaluated by an investigator on seriousness, severity and causality. All adverse events (AEs) and serious adverse events (SAEs) causally related to a study-related intervention were reported until last (follow-up) visit. All SAEs as defined in the protocol needed to be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event.

## STATISTICS AND ANALYSIS

Statistical methods for this Proof of Concept study focused on the practical evaluation of UC in general practice. Because this was a small study, the use of statistics was limited. We used descriptive statistics to become success rates, contamination rates and time-efficiency. Interviews were analyzed thematically to identify common themes and patterns.

Because this was a Proof of Concept study for UC in children in general practice, the study did not include a large number of participants. Therefore we started with a small group of ten GPs, which each tried to include as much children as possible. Because we provided 5 UC kits to every GP, we aimed to include 5 participants per GP, corresponding to a sample size of 50 children.

The study staff pseudonymized the participants' data into RedCap. All documents were stored securely and were only accessible by study staff and authorized personnel.

# RESULTS

## CHARACTERISTICS OF THE INCLUDED GENERAL PRACTITIONERS

Of the 10 participating GPs, 4 GPs worked at Huisartsenpraktijk De Ceder (Schilde), 3 GPs at Huisartsenpraktijk Den Els (Oelegem), 2 GPs at Huisartsenpraktijk Linden (Linden) and 1 GP at Huisartsenpraktijk De Akkerhoorn (Zedelgem). These participating sites were all located in a semi-rural to rural area and were all group practices. The age of the GPs ranged from 27 to 58 years old (median age 36,5 years old). 4 of the included GPs were men and 6 were women. Years of experience (including years of training) as a GP varied from 2 to 34 years (median 10,5 years), one GP was still in training.

## PATIENT CHARACTERISTICS

Only one GP included a participant, i.e. the same child at two different illness episodes. The patient was a Caucasian girl, not yet toilet trained and her age was 18 months at first presentation and 20 months at the time of the second inclusion. She had a history of vesicoureteral reflux (VUR) but was not on chronic medication. She was accompanied by a parent on both occasions.

## URINE COLLECTION RESULTS

It was not possible to collect a clean-catch sample (success rate 0/2). The first time the patient urinated spontaneously, but the GP was not able to collect the urine in a sterile container.

Catheterization was successful in both attempts (success rate = 2/2), although the GP mentioned that it was not simple to find the urethra the first time. Time-to-collection (starting from opening the UC kit to closing the sterile container) improved markedly at the second attempt, i.e. from 9 minutes 30 seconds to 4 minutes and 9 seconds. Both urine cultures came back negative, meaning there was no contamination (contamination rate = 0/2).

Antipyretics were recommended as treatment in both cases. Parents' opinions were positive because a visit to the emergency department for a catheterized urine sample was avoided, which is even more beneficial during the infection season. No adverse or serious adverse events were reported.

## QUESTIONNAIRE AT THE START OF THE STUDY

Prior to the introduction of the study, most of the GPs assumed that the clean-catch method is theoretically the best way to collect a urine sample in non-toilet trained children in general practice (n = 8). Only a few GPs thought UC is the preferred method (n = 2). Some GPs also mentioned other collection methods such as urine bags (n = 2) or UC (n = 1) as alternatives for the clean-catch method. In practice, urine bags were still the most used collection method (n = 10), only 2 GPs attempted collecting a clean-catch sample first (n = 2). All GPs knew how to collect a clean-catch urine sample, but only one of them had tried it before by using the Quick-Wee method (n = 1), however the attempts were not successful. A few GPs had already tried to explain the clean-catch method to the parents so they could try it at home or in the restroom of the practice (n = 3).

All GPs assumed that we as doctors are capable of performing UC on pre-continent girls and boys (n = 10). However, they immediately mentioned some prerequisites and concerns. First they need information and training on how to do it, secondly it needs to be time-efficient, it also needs to be organizable (parent or colleague available) and last the indication needs to take place on a regular basis in order to master the skill. Opinions on what is the best way to teach UC were divided. The preferred training method was a theoretical explanation combined with exercising on practice dummies (n = 5), other suggestions were video's (n = 2) or a real coaching in a pediatrics department (n = 4).

The majority assumed that it would take the same amount of time or even less time if you master and maintain the skill of urinary catheterization well, especially compared to urine bags (n = 7). Explaining urine bags to parents and/or waiting until they collected it at home and brought it back to the practice, can be very time-consuming. On the other hand some GPs thought it will take more time, if you do not have the material close by or you need to wait for a colleague to help (n = 3). They also think it will need more explanation to the parents (n = 2). One GP suggested that a nomenclature number could be a compensation for the additional time.

If they mastered UC well, most of the GPs would proceed more quickly to UC in order to collect a urine sample, because you have a more direct and reliable sample (n = 8), if the cost of the material is acceptable. One GP did not think it will be necessary because it is not common and the clean-catch method by parents usually succeeds (n = 1). Another GP will not prefer UC because the wellbeing of the child takes precedence (n = 1).

All doctors agreed that a urine sample obtained by UC will have lower contamination rates than non-invasive techniques (n = 10). They assumed there would be a positive impact of UC on the diagnosis of UTI in general practice from fewer false positive urine cultures (n = 3), a gain in efficiency (n = 3), a faster and more reliable diagnosis (n = 3) and a more targeted use of antibiotics (n = 3).

The most mentioned barrier for UC was the lack of hands-on experience because of the low incidence (n = 8). Other barriers were the time it will take (n = 4), the resistance of the parents (n = 2), the need of having the presence of parent who can help (n= 2), the fear of traumatizing the child (n = 1), and having the right material available (n = 1).

## QUESTIONNAIRE AT THE END OF THE STUDY

Because the majority of the GPs had not included any participant, their experience with the clean-catch method and UC remained unchanged (n = 9). There were different opinions on the role of the clean-catch method in general practice in the future, most GPs mentioned it as the method of first choice (n = 6) but they also saw it as more time-consuming and there is no guarantee of success. Therefore one GP would prefer UC now he knows how to do it (n = 1). The GP who effectively tried the clean-catch method during the study, experienced it as unsuccessful and concluded it to be of little use in general practice (n = 1). A different opinion is focusing on the clean-catch as a method to give along with the parents by using a flyer or instruction video (n = 1).

Most GPs experienced the training and teaching as interesting, structured, clear and sufficiently detailed (n = 8), some suggested a practice dummy might be useful (n = 2). They mentioned that we should be capable of performing UC in pre-continent children, given the right training and that the indication presents itself regularly (n = 8). 2 GPs made a distinction based on sex, one GP only performed it on a girl and therefore did not make a statement on UC in boys (n = 1). Another GP expressed a concern about the more difficult anatomy in boys (n = 1).

The one GP who performed UC twice experienced a steep learning curve. The first time, the GP experienced it as difficult, but the second time it was much easier and it took less than five minutes. The GP found this positive compared to the unsuccessful clean-catch and the time you spend explaining a urine bag. This GP experienced the provided materials as convenient to use. Among the other GPs, there were some of them who mentioned the materials seemed to be of good quality and easy to use (n = 4). Another GP liked the idea of a UC kit, because it can lower the barrier to perform UC in practice (n = 1).

The UC was experienced as positive by the parents (n = 1).

The minority of the GPs would switch to UC to collect a urine sample in the future more quickly (n = 4). The other part of the GPs would not apply this method in the future because they did not gain experience with it during the study (n = 6). In contrast, most GPs mentioned UC as a valuable option and useful tool to reduce referrals to secondary care (n = 7). But again they added some conditions, you have to master it well and it will only be useful in specific situations (fever without initial focus, personal history of UTI or an existing predisposing condition as VUR). The other GPs found UC not beneficial because of the low prevalence in general practice (n = 3).

In order to keep utilizing UC in the future, GPs found it necessary to regularly use it in daily practice (n = 5). Taken into account the low prevalence experienced during the study, one GP suggested it can be useful to appoint one UC expert in a group practice (n = 1). Other GPs felt a need of frequent refresher courses, were it is also possible to exercise this technique on practice dummies (n = 6). A video or step-by-step plan on how to do it was experienced as useful to rehearse the theory in advance of performing UC (n = 3). As mentioned before a nomenclature number could be an additional motivation to continue doing UC in general practice (n = 1).

In conclusion, there were different opinions about the future of urine collection methods in general practice. Some of the GPs considered UC as a valuable alternative or second option to the clean-catch method (n =4). Other GPs would invest more in the clean-catch method as a home method done by parents (n = 2). A few GPs did not see UC as an option because of the perceived low prevalence (n = 4) and some of them resigned themselves to the urine bags (n = 3). One GP suggested UC can be valuable at an out-of-hours GP service, if the right materials are provided (n = 1).

## INTERVIEWS AT THE END OF THE STUDY

All the GPs agreed on the reason why the total number of inclusions was that low, they attributed this to a low prevalence of UTI in general practice. They suggested a longer study inclusion period in order to prevent a season phenomenon by not running the study only during the infection/winter season (n = 5). Most GPs considered the study as feasible because of the good explanation/training and organization (n = 6). One GP mentioned that C-reactive protein (CRP) point-of-care testing could help in diagnostic uncertainty and was considered as more applicable than UC (n = 1).

# DISCUSSION

This interventional study combined with a nested interview study investigated whether UC is feasible in general practice as a urine collection method for the diagnosis of UTI in non-toilet trained children. Of the 10 GPs included across Flanders, only one included a participant; the same patient was included twice. These results were in contrast with the pre-existing thoughts of the GPs on UC. All GPs were convinced that family doctors are capable of performing UC and most of them thought they would proceed more quickly to UC as urine collection method knowing it will result in a more reliable urine sample. Questionnaires and interviews revealed that GPs set certain conditions that must be met in order to implement UC in general practice.

## PREVALENCE OF UTI IN GENERAL PRACTICE

The first and foremost condition is that the indication for a urine sample must occur frequently enough in order to master the skill. The main reason given by the GPs for the low number of inclusions was a perceived low prevalence, nine of the included GPs had no single potentially eligible participant during the study period. For some GPs this outcome is sufficient reason to conclude that UC is not feasible in general practice. We compared this perceived low prevalence with the existing literature. In general practice, the prevalence of UTI in acutely ill children below 5 years old is approximately 6% (27,28). A systematic review, not restricted to general practice, concluded there is an overall prevalence of UTI of 7% in febrile infants, with the highest prevalence in girls less than 12 months of age and uncircumcised boys less than 3 months of age (5).

A question that can be raised is whether GPs give enough thought to UTI in their clinical decision making. In primary care up to half of the UTIs can be missed during the first assessment, because ruling out UTI in non-toilet trained children is challenging due to the non-specific clinical features (27,29). There exists no single symptom or clinical feature that is able to rule out UTI (28). If we take a look at the urine sampling rate in acutely ill children in primary care, it is only 1% (4,30). In general practice it is undesirable to obtain a urine sample in all children, but guidelines lack very specific descriptions about when urine sampling is recommended. In our study we focused on obtaining a urine sample from non-toilet trained children presenting with unexplained fever (< 2 years old), as mentioned in the guidelines (6,8,10,24). A recent systematic review showed that urinary tract infections can not be ruled out when clinical features suggest another focus such as a respiratory tract infection (cough, rhinitis, …) (28). Therefore sampling only children with fever without focus leads to missed diagnoses. This under-detection of UTI could also be present in our study.

For the future of ruling out UTI in primary care, there is a need of further validation of clinical prediction rules (for example DUTY score, UTICalc, Gorelick score), combining clinical features and symptoms to select children at risk of UTI (28,30,31). In addition novel point-of-care tests and urine collection methods for obtaining a reliable sample during the consultation, are necessary (28,30,31).

## URETHRAL CATHETERIZATION EDUCATION AND TRAINING

Education and training on how to perform UC was a second condition for GPs to apply UC in general practice. Despite that all GPs were convinced that they were capable of UC, it is remarkable that UC in children is not taught during basic medical training in Belgium. We were trained in UC in adult men and women by using practice dummies. Perhaps children need to be integrated as well in medical education in the future, this could possibly lower the threshold.

Although most GPs mentioned the training session at the start of the study interesting, well structured and clear, dummies to practice UC were often suggested in both questionnaires. In advance of the study we tried to borrow practice dummies. However the university of Antwerp and Leuven had no children/infant practice dummies for UC. The Karel de Grote University of applied sciences and arts did have an infant practice dummy, but were not allowed to lend it to us. We informed also at Domus Medica who also did not have any practice dummies.

Because GPs will not perform UC on a daily basis, they clearly expressed a need for refresher courses, video or other learning materials where they can refer back to if they perform UC.

## URETHRAL CATHETERIZATION IN BOYS COMPARED TO GIRLS

There was some concern about the difference in difficulty level of UC between boys and girls. Performing UC in boys was perceived as more difficult, raising the barrier in general practice. Uncircumcised boys under 3 months of age have a high baseline prevalence of UTI (5), but this is a population GPs would rather refer to the pediatrician if UTI is suspected. This could lower the need of UC on boys in general practice. In addition, girls are 3 times more likely to have a UTI, if there is a significant suspicion for it (3,4). Therefore it could be considered to only perform UC on girls in general practice.

## TIME-EFFICIENCY

In advance of the study there were different opinions on how much time UC will take during a consultation. Because our sample size was too small, we can not make any big conclusions. However, the learning curve of the GP who performed it twice was remarkable. The second time it only took less than half the time of the first catheterization, more specifically 4 minutes and 9 seconds. Compared to waiting for a clean-catch or explaining a urine bag/clean-catch to the parents to do it home, it is not that time-consuming and more reliable. To maintain this time-efficiency it is important to regularly practice UC. An interesting suggestion was to appoint a UC expert who can do all the catheterizations in a group practice and can properly master the skill.

## MATERIAL AND COSTS

The material needed for UC is rather limited and therefore easy to add to the stock of a GP practice. Again, there are some conditions, just like in our study GPs like to have all the materials together in a UC kit, so there is a minimal loss in time. A second concern is the cost. A cost-effectiveness analysis (in the emergency department) concluded UC as the most cost-effective urine collection method (32). Of the non-invasive techniques voiding stimulation was the most cost-effective method and urine bags the most expensive method (32). In practice, GPs receive these urine bags free of charge from the local laboratory. In contrast, GPs will have to pay for a urethral catheter themselves (price of the SpeediCath® Child is approximately 2.7 euros per catheter), unless it can be provided by the laboratory as well in the future.

## PARENTAL PERCEPTION

In order to perform UC in general practice, the presence of an adequate parent or guardian who is capable to hold and comfort the child is needed. In reality not every parent will be able to fulfill this role, meaning the GP will have to rely on a colleague or nurse who is not always available.

Another concern mentioned by the GPs at the start of the study was the perception of the parents. The parents of the patient included in our study were positive about UC, because there was a personal history of VUR and by performing UC in general practice a visit to the emergency department was avoided. A cross-sectional survey highlighted that parental factors could have a substantial impact on adherence to the guidelines in the evaluation of a suspected UTI in their children (9). For example, UC was more likely to be offered to parents with a college education, but these parents were also more likely to associate UC with extreme distress and therefore less likely to give consent for UC (9). For the future it is important to not only educate physicians of correct practices and guidelines of UTI, but also the parents (9).

In literature, comparing UC to a bladder stimulation technique for the clean-catch method resulted in an improved parental and provider satisfaction when using bladder stimulation (33). During bladder stimulation parents experienced less discomfort than during UC (33). As mentioned in our literature search, there is not yet enough evidence for stimulation techniques, further research is necessary.

## LIMITATIONS AND OTHER CONTRIBUTING FACTORS TO OUR SMALL SAMPLE SIZE

As proof of concept study we aimed for a small sample size of 50 children, meaning every GP would have to include 5 children. The study period was rather limited (up to 5 months) due to deadlines of the Master of Family medicine and the large amount of time needed to get approval by the Clinical Trial Center UZ Leuven and the Ethics Committee Research UZ/KU Leuven. As also suggested by the participating GPs, a longer study period including all seasons could have resulted in a higher number of inclusions. Nevertheless, the very low inclusion rate suggests important barriers to performing UC in general practice.

One GP mentioned the use of a CRP point-of-care test as a possible explanation of the low number of inclusions. Collecting a droplet of blood in children by finger prick testing is an easy, rapid and accurate way to measure the CRP. It seemed more low threshold than collecting a urine sample in pre-continent children. A systematic review on the diagnostic accuracy of biomarkers in UTI concluded that an inflammatory marker such as CRP can be useful for ruling out pyelonephritis (CRP < 20 mg/L), but is of little additional value for cystitis (34).

# CONCLUSION

In conclusion, UC in itself is a reliable and efficient urine collection method which should be feasible in general practice. Despite the fact that UC was theoretically welcomed by all GPs, its applicability in general practice seemed limited. The main condition to continue using UC is that the indication needs to present itself regularly in order to master the skill, otherwise GPs feel not confident enough. In addition, clinical prediction rules are needed to decide when to obtain a sample.

In practice, urine bags are still the most used method although GPs know that they give high contamination rates and are not recommended in the guidelines. A clean-catch sample is the most reliable non-invasive technique, but it can be time-consuming an messy. The experience of the included GPs with this urine collection method was rather low and the attempts during the study were unsuccessful. Given the low contamination rates comparable to UC, the cost-effectiveness and the non-invasive character, this technique can be more suitable as method of first choice in primary care. However, there is a need of a better education on this method and more research is necessary on how to make it more feasible in general practice. Options to consider for the future can be bladder stimulation techniques or a home clean-catch sample obtained by parents after giving the right instructions.

# FUNDING

KU Leuven was the sponsor of this study. All the materials needed for urethral catheterization were provided by the local laboratory A.M.L. Antwerp.

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# APPENDIX

## APPENDIX 1 – SEARCH STRING

("Urine Specimen Collection"[Mesh] OR "urine collection"[tiab] OR "clean-catch urine collection"[tiab] OR "quick wee method"[tiab] OR "suprapubic aspiration"[tiab] OR "bladder stimulation"[tiab] OR "urine bag"[tiab] OR "transurethral bladder catheteri*"[tiab] OR "urinary catheteri*"[tiab] OR "urethral catheteri*"[tiab]) AND ("Infant, Newborn"[Mesh] OR "Infant"[Mesh] OR "non-toilet-trained children"[tiab]) AND ("Diagnosis"[Mesh]) AND ("Urinary Tract Infections"[Mesh] OR "cystitis"[tiab] OR "pyelonephrit*"[tiab])

# APPENDIX 2 – ETHICAL APPROVAL

UZ LEUVEN

Leuven, 30 Aug 2024

**Ethics Committee**
**Research UZ/KU Leuven**
Herestraat 49
B 3000 Leuven (Belgium)
Tel +32 16 34 86 00
Email : ec@uzleuven.be

prof. dr. Ann Van den Bruel

| Our reference: | EudraCT-nr: | Belg. Regnr: |
|---|---|---|
| S68066 | | B3222024001440 |

**Is urethral catheterization as urine collection method in young children feasible in general practice ? A proof of concept study.**

**Positive advice** in accordance with the law of 7 May 2004 on experiments on the human person

Dear colleague

The Ethics Committee Research (EC Research) UZ/KU Leuven has examined and discussed the above mentioned dossier in the meeting held on 12 Aug 2024.

After having consulted the additional information and/or adapted documents relating to this dossier, EC Research considers that the proposed study, as described in the protocol, is scientifically relevant and ethically justified. It therefore gives on 30 Aug 2024 a favourable opinion of this study.

EC Research emphasizes the responsibility of the PI/promotor of this study concerning the privacy of the participants'/patients' data. Additionally, all access to patient data by students or coworkers should occur under the responsibility and supervision of the PI/promotor (including the use of personal data in electronic/digital tools).The PI/promotor is responsible for the implementation of the project proposal in accordance with applicable laws and regulations including, but not limited to, the EU regulation 2016/679 (General Data Protection Regulation), the Belgian Law on patients' rights of 22/8/2002, and the policy of the institution where the research will be carried out.

EC Research refers to the ICH/GCP guidelines on its website, and confirms that a GCP-training is required for each investigator. It is the responsibility of the principal investigator that each member of the study team has a valid GCP-certificate (i.e. a certificate obtained not longer than 3 years ago).

EC Research underlines the sponsor's responsibility for the use of the application/digital tool in this clinical study. More specifically, the sponsor should conduct all essential GDPR checks to make sure the use of this application/tool is justified, GDPR compliant



and safe for the processing of sensitive personal data.

The patient should be well informed about the terms, conditions and costs of application. Furthermore, the sponsor's obligations should not be compromised by these terms and conditions, especially in terms of privacy protection of the patient. Please inform the patient about additional costs (if any) that are linked to the usage of the application/tool. This information should be added to an updated ICF, if necessary, in a subsequent amendment to the study.

Finally, EC research emphasizes that only essential data for the purpose of the application/tool can be collected (cf. GDPR principle of data proportionality and minimization).

For the assessment of this dossier, documents/answers received on 09 Apr 2024, 01 Aug 2024 , 21 Aug 2024 and 30 Aug 2024 have been taken into account.

The favourable advice concerns:

*Protocol:*
version 3.2 dd 30Aug2024
*Informed Consent Form:*
ICF v2.0 dd 13Jun2023 Nl
*Other subject information documentation:*
vragenlijst PRE en POST v1.0 dd 13aug2024 Nl
*Proof of "no-fault" insurance cover:*
dd 01Jan2024 - 31Dec2024
*Recruitment material:*
flyer versie 1.0 dd 07May2024 Nl
*GDPR questionnaire:*
dd 20Jul2023 + PRET accepted dd 21aug2024

EC Research confirms working in accordance with the ICH-GCP principles (International Conference on Harmonization Guidelines on Good Clinical Practice), the latest version of the Declaration of Helsinki, the Oviedo Convention on Human Rights and Biomedicine and applicable laws and regulations.

EC Research confirms that members with a potential conflict of interest abstain from voting.

List of members: see appendix.

Points of concern: (if applicable)

*The conformity of translated documents compared to the Dutch documents, is the responsibility of the sponsor.*

*We would like to draw your attention to the fact that EC Research expects her initial comments to be taken into account ab initio at the next submission by the same sponsor.*



*Provided that there is a **Clinical Trial Agreement**, the study can only start when the Clinical Trial Agreement has been approved and signed by the CEO of UZ Leuven (and/or by an authorized representative of KU Leuven R&D).*

*Please take into account the regulations of the hospital concerning tissue management and the regulations of the law of December 19, 2008.*

*It is important to note that approval from EC Research is required for all use of e-consent before the process can start. This is a crucial step to ensure that all ethical considerations and regulations are adhered to. For more detailed information regarding the policy and procedure concerning e-consent in REDCap, we kindly refer you to the specific page on the CTC Datamanagement website: https://gbiomed.kuleuven.be/english/ctc/intern/data-management/econsent*

*This favourable advice from EC Research does not imply that EC Research can be held accountable for the planned study. You will remain responsible for the study. In addition, you should ensure that your opinion as principal investigator is reproduced in publications of study results, reports for the government, etc.*

*The EC approval granted for a specific project, is valid for one year.*

*If the study will not be terminated within a year, the ICH-GCP demands that an **annual progress report** will be provided to EC Research. . We also request you to inform us if the study will not be initiated or if the study does not start within 1 year after approval.*

*Finally, the termination (early or planned) of the study should be reported within the legal deadlines.*

Yours sincerely,

Prof. Dr. Minne Casteels
Chair
Ethics Committee Research UZ Leuven

Cc:
**FAMHP** (Federal Agency for Medicines and Health Products)

**CTC** (Clinical Trial Center UZ Leuven)



**List of members EC Research UZ/KU Leuven**

| | | |
|---|---|---|
| Chair | prof. dr. Maria-Reinhilde Casteels | Clinical Pharmacology |
| Vice chair | prof. dr. Dominique Bullens | Paediatrics |
| | De heer Aernout De Raemaeker | Medical Legislation alternate |
| | De heer Jean-Jacques Derèze | Medical Legislation alternate |
| | De heer Mathijs Swaak | Healthy volunteer repres. |
| | Mevr. Annick Vanclooster | Nurse |
| | Mevr. Dorien Fierens | Medical Legislation alternate |
| | Mevr. Katelijne Van Overwalle | Pt representative (alternate) |
| | Mevr. Lia De Wilde | Pt representative (alternate) |
| | Mevr. Marie Gilliot | Medical Legislation alternat |
| | Mevr. Marilien Vandeputte | Nurse |
| | Mevr. Teresia De Fraye | Pt representative |
| | Mevr. Valerie Christens | Medical Legislation alternat |
| | Mevr. Veerle Vanparys | Pharmacist (alternate) |
| | dr. Ellen Deleus | Abdominal surgery |
| | dr. Kamiel Verbeke | Clin. Psychology |
| | dr. Lut De Groote | General Practitioner |
| | dr. Marleen Renard | Paediatrics |
| | dr. Walter Janssens | Clinical Pharmacology |
| | prof. André Loeckx | Pt representative (alternate) |
| | prof. Ben Van Calster | Statistics |
| | prof. Guy Bosmans | Clin. Psychology (alternate) |
| | prof. Kristin Verbeke | TARGID |
| | prof. Pascal Borry | Ethics (alternate) |
| | prof. Rik Gosselink | Revalidation |
| | prof. dr. Anne Smits | Paediatrics |
| | prof. dr. Anne Uyttebroeck | Paediatrics |
| | prof. dr. Ariel Alonso | Statistics (alternate) |
| | prof. dr. Bart Van der Schueren | Endocrinology / Pharmacology |
| | prof. dr. Catherine Cassiman | Ophthalmology |
| | prof. dr. Francesca Bosisio | Pathology |
| | prof. dr. Frank Van Calenbergh | Neurosurgery |
| | prof. dr. Frederik Nevens | Hepatholgy |
| | prof. dr. Gregor Verhoef | Haematology |
| | prof. dr. Jan Verhaegen | Laboratory Medicine |
| | prof. dr. Jan de Hoon | Clinical Pharmacology |
| | prof. dr. Karin Sipido | Experimental Cardiology |
| | prof. dr. Koen Luyckx | Clin. Psychology (alternate) |
| | prof. dr. Laura Van Gerven | ORL |
| | prof. dr. Maria Schetz | Intensive care |
| | prof. dr. Peter Sinnaeve | Cardiology |
| | prof. dr. Simon Brumagne | Physiotherapy |
| | prof. dr. Xavier Bossuyt | Immunology |
| | prof. dr. apr. Erwin Dreesen | Pharmacist |

# APPENDIX 3 – QUESTIONNAIRES AND INTERVIEW

## APPENDIX 3.1 – QUESTIONNAIRE PRE

1. Hoe wordt theoretisch het beste urine opgevangen voor de diagnose van urineweginfecties bij kinderen in de huisartsenpraktijk?
2. Hoe gebeurt de opvang van urine bij kinderen in uw huisartsenpraktijk?
3. Weet u wat de clean-catch methode inhoudt en bent u hiermee vertrouwd als huisarts?
4. Denkt u dat wij als huisarts in staat zijn om jongens en meisjes die niet zindelijk zijn te sonderen (met de nodige opleiding) en wat is uw mening hierover?
5. Wat is uw mening over het aanleren van urethrale katheterisatie, hoe denkt u dat dit zou verlopen?
6. Wat denkt u over de tijd die sonderen in het beslag neemt tijdens een consultatie in vergelijking met andere niet-invasieve methoden?
7. Indien u het sonderen goed zou beheersen, zou dit voor u een methode zijn die u dan sneller zal toepassen, waarom wel of waarom niet?
8. Wat denkt u over de contaminatie van urinestalen bekomen door urethrale katheterisatie in de huisartsenpraktijk en het belang hiervan?
9. Welke impact denkt u dat sondage kan hebben op de diagnose en het uitsluiten van urineweginfecties bij jonge kinderen in de huisartsenpraktijk?
10. Wat zijn voor u mogelijke drempels voor het uitvoeren van urethrale katheterisatie in de huisartsenpraktijk?

## APPENDIX 3.2 – QUESTIONNAIRE POST

1. Tijdens de studie werd er aangeraden om eerst urine op te vangen met de clean catch methode, wat is uw ervaring hiermee na afloop van de studie?
2. Hoe ziet u het gebruik van de clean catch methode als opvangmethode voor urine bij niet zindelijke kinderen in de toekomst binnen uw huisartsenpraktijk.
3. Hoe verliep het aanleren van urethrale katheterisatie?
4. Vindt u dat wij als huisarts in staat zijn om zowel niet-zindelijke jongens als meisjes te sonderen voor het bekomen van urine, waarom wel of waarom niet?
5. Hoe was uw leercurve van transurethrale katheterisatie als huisarts?
6. Hoeveel tijd nam het bekomen van een urinestaal via urethrale katheterisatie in beslag in vergelijking met andere niet-invasieve methodes?
7. Hoe zou u in de toekomst urethrale katheterisatie toepassen als huisarts voor de diagnose van urineweginfecties bij niet-zindelijke kinderen, nu u deze techniek goed beheerst? Zou u sneller overgaan tot het zelf afnemen van een urinestaal?
8. Hoe vond u het materiaal voor het uitvoeren van de sondage? Was het makkelijk hanteerbaar? Is het iets dat we standaard aan het materiaal in een huisartsenpraktijk kunnen toevoegen?
9. Wat was de impact van katheterisatie op het effectief bekomen van een urinestaal, kon u makkelijker een urinestaal verzamelen dan bij gebruik van niet-invasieve methoden?

10. Hoe betrouwbaar waren de resultaten van de urinecultuur? Was er veel contaminatie?
11. Hoe ervaarden de ouders de katheterisatie bij hun kind? Hoe reageerden ze?
12. Welke plaats ziet u voor urethrale katheterisatie in de huisartsenpraktijk als urine opvangmethode bij niet zindelijke jongens en meisjes? Is het een meerwaarde?
13. Wat denkt u dat er nodig is om in de toekomst het sonderen te blijven toepassen? Zijn er zaken die de drempel nog verder zouden kunnen verlagen? Nood aan opfrissingscursussen?
14. Hoe ziet u de toekomst van urine opvangmethoden voor de diagnose van urineweginfecties bij niet-zindelijke kinderen?

## APPENDIX 3.3 – INTERVIEW AT THE END OF THE STUDY

1. Vond u zelf dat u voldoende kindjes heeft kunnen includeren? Zo niet, waaraan lag dit dan volgens u?
2. Heeft u nog andere opmerkingen, bedenkingen of inzichten bij de studie, haar verloop of de haalbaarheid ervan?

# APPENDIX 4 – STEP-BY-STEP INSTRUCTION ON URETHRAL CATHETERIZATION







Sources of the images and videos used:

- https://images.app.goo.gl/vqKds8WXFH6ho2Q46
- https://images.app.goo.gl/mE87rxxWigPuXWVn9
- https://images.app.goo.gl/e7qY9d26rckvQTzE6
- https://images.app.goo.gl/E96k3c9kZnxj669W6
- https://images.app.goo.gl/tc1SGgi5z4bc4FRZ9
- Print screen of https://www.youtube.com/watch?v=0pGzMsphado
- Print screen of https://www.youtube.com/watch?v=BcOOHMA6AOQ
- Video UC boys: https://www.youtube.com/watch?v=nVldql6f79Q&list=PL7DwlsPlf2Us3__A28sVpkSjYptflbAoM
- Video UC girls: https://www.youtube.com/watch?v=qmCyH3X1VtA&list=PL7DwlsPlf2Us3__A28sVpkSjYptflbAoM&index=2

# APPENDIX 5 – RECRUITMENT OF PARTICIPANTS

## Recruitment of participants

### Selection process of general practitioners

General practitioners will be recruited via the Domus Medica newsletter and direct contact via email. We will select 10 GPs from those expressing interest using purposive sampling if possible, ensuring we include GPs of different ages, practice types and practice location (rural vs urban).

The following mail/advertisement (in Dutch) will be used:

Masterproef: Urethrale katheterisatie als urine opvangmethode voor de diagnose van urineweginfecties bij jonge kinderen in de huisartsenpraktijk.

*Beste arts,*

*In kader van mijn masterproef voor de master na master opleiding huisartsgeneeskunde ben ik nog op zoek naar artsen/huisartsenpraktijken die bereid zijn om deel te nemen aan mijn onderzoek.*

*Het betreft een "proof of concept" studie die wil nagaan of er in de huisartsenpraktijk een plaats is voor eenmalige sondage als urine opvangmethode bij kinderen.*

*Kort samengevat willen wij met deze studie bijdragen aan een correcte diagnose van urineweginfecties bij niet-zindelijke kinderen. Heden zien we dat er in de praktijk vooral gebruik wordt gemaakt van kleefzakjes, echter gaat dit gepaard met een grotere kans op contaminatie. Daarnaast zijn de betere niet-invasieve methoden vaak omslachtig en niet efficiënt. In ziekenhuizen zal men sneller overgaan tot urethrale katheterisatie, wat ook volgens de richtlijnen de meest betrouwbare techniek is voor een urinestaal te bemachtigen bij deze niet-zindelijke populatie. Vandaar onze vraag naar de toepasbaarheid hiervan in de huisartsenpraktijk.*

*Het is een eerste, kleinschalige studie waar huisartsen de techniek zullen aangeleerd krijgen en nadien hun bedenkingen aan de hand van een vragenlijst kunnen meedelen. Zo krijgen we een zicht op de toepasbaarheid en kan dit een eerste stap zijn naar een meer betrouwbare urine opvangmethode in de huisartsenpraktijk.*

*Zo u hierover nog bijkomende vragen heeft of graag wenst deel te nemen, mag u me steeds contacteren op het volgende e-mailadres: evy.debeys@student.kuleuven.be*

*Alvast bedankt,*

*Evy De Beys, huisarts in opleiding*

*Prof. Dr. Ann Van den Bruel, promotor*

### Selection process of participating children

The participating general practitioners will be in charge of the election of the participating children, more information can be found in the protocol.

The GP will approach the parents during the consultation to check if they meet the inclusion criteria. If they are eligible, the GP will seek for a written informed consent.

To inform parents/guardians of children (between 3 months and 2 years) about the study, there will be information sheets available in the waiting room of the practice, potentially handed out by a non-clinical staff member such as a receptionist. There will also be a poster displayed in the waiting room.

For both the poster and the information sheets we will be using the following layout.



KU LEUVEN

Academisch Centrum voor Huisartsgeneeskunde

## Uw huisarts werkt mee aan een studie van de KU Leuven over een betere diagnose van urineweginfecties bij kleine kinderen.

Het is belangrijk om een goed urinestaal te kunnen onderzoeken als de huisarts vermoedt dat een kindje een urineweginfectie heeft. Bij kindjes die nog niet zindelijk zijn, gebruikt de huisarts daarom zakjes die op de huid rond de plasbuis worden geplakt. Deze zakjes zijn lastig om te gebruiken en de urine is vaak niet zuiver genoeg door het contact met de huid.

In het ziekenhuis wordt daarom bij kleine kindjes urine opgevangen via een blaassonde. Ook in de richtlijnen voor huisartsen staat dat dit een goede manier is om een zuiver urinestaal te bekomen. In deze studie gaan we na of dit in de huisartspraktijk ook echt haalbaar is. Alle deelnemende huisartsen werden speciaal opgeleid voor het gebruik van deze sondes. Het onderzoek vindt plaats onder leiding van Prof. Dr. Ann Van den Bruel en werd ook goedgekeurd door het ethisch comité van de KU Leuven (S68066/ B3222024001440).

Voor meer informatie en vragen kan u terecht bij uw huisarts.

APPENDIX 7 – CLINICAL RESEARCH PROTOCOL 30 AUGUST 2024 VERSION 3.2

# Study title: Is urethral catheterization as urine collection method in young children feasible in general practice ? A proof of concept study.

Date and version no: 09 November 2023, version 3.0


Chief investigator: Prof Dr Ann Van den Bruel, Academisch Centrum voor Huisartsgeneeskunde, KU Leuven, Kapucijnenvoer 33 blok J, 3000 Leuven

Investigators: Dr An Van Adorp, Academisch Centrum voor Huisartsgeneeskunde, KU Leuven, Kapucijnenvoer 33 blok J, 3000 Leuven

Dr Evy De Beys, Academisch Centrum voor Huisartsgeneeskunde, KU Leuven, Kapucijnenvoer 33 blok J, 3000 Leuven



Sponsor: KU Leuven

Funder: None


All investigators declare they have no conflicts of interest that could impact the integrity of the study.

**Confidentiality Statement**

The information in this document is strictly confidential and disclosure to anyone other than the investigator team, host organisation and members of the Research Ethics Committee is not allowed, unless they are authorised to do so.

# SYNOPSIS

| | | |
|---|---|---|
| **Study Title** | Is urethral catheterization as urine collection method in young children feasible in general practice ? A proof of concept study. | |
| **Internal ref. no. / short title in Dutch** | Urethrale katheterisatie als urine opvangmethode voor de diagnose van urineweginfecties bij jonge kinderen in de huisartsenpraktijk. | |
| **Study Design** | An interventional study combined with a nested interview study | |
| **Study Participants** | - Pre-continent children aged 3 months to 2 years in whom a urine sample is deemed necessary by the treating physician<br>- General practitioners in Flanders | |
| **Planned Sample Size** | - 50 children<br>- 10 general practitioners | |
| **Planned Study Period** | 01/09/2024-28/02/2025 | |
| | **Objectives** | **Outcome Measures** |
| **Primary** | To assess the success rate of urethral catheterization as urine collection method for diagnosing urinary tract infections in pre-continent children aged between 3 months and 2 years. | Success rate |
| **Secondary** | 1. To assess the rates of contamination of urethral catheterization when performed in general practice.<br>2. To assess how time-consuming urethral catheterization is in a family doctor's office.<br>3. To describe how the family doctors experienced the implementation of urethral catheterization in general practice. | 1. Contamination rate<br>2. Time efficiency<br>3. Descriptive |

# ABBREVIATIONS

| | |
|---|---|
| GP | General practitioner |
| UC | Urethral catheterization |
| UTI | Urinary tract infections |
| CRF | Clinical report form |
| (S)AE | (Serious) adverse event |
| AR | Adverse reaction |

# BACKGROUND AND RATIONALE

The diagnosis of urinary tract infections (UTI) in children who are not yet toilet-trained is challenging. On the one hand because of the non-specific presentation at young age and on the other hand because it is difficult to obtain a reliable urine sample at this age[1,2]. The overall prevalence of UTI in young children presenting in primary care with fever (above 38°C) is 7%[2]. Correct and early diagnosis is very important because when these UTI remain undetected, they can cause several complications, example given renal scarring, renal failure or systemic infections[1]. Therefore diagnosing UTI in pre-continent children in primary care is important. In order to do this, we need an accurate urine sample, this can be obtained by several urine collection methods. European and American guidelines recommend suprapubic aspiration and urinary catheterization (UC) as the gold standard, these are both invasive methods but they are associated with lower contamination rates[2,3]. This is even more important in acutely ill children in which antibiotics need to be started empirically, because an accurate sample is needed to adjust the antibiotics to the pathogen. The most reliable non-invasive method is a clean-catch urine collection, this technique has a contamination rate of 5% which is comparable to UC[1]. Therefore a clean-catch urine is a good and low-threshold alternative for UC in general practice. In reality this technique is time consuming and messy[1,3]. Recent studies tried to enhance the clean-catch method by using a cold compress to stimulate urine voiding (the "Quick-Wee method"). This resulted in a more successful urine collection within 5 minutes, but even then it only worked in a minority of patients (30%)[1]. Because the reliable non-invasive methods are time consuming, we suggest that maybe UC can be a more efficient and accurate alternative in general practice for collecting a sample in pre-continent children in which it is not possible to obtain a clean-catch spontaneously.

The objective of this study is to explore whether UC is feasible in general practice for the diagnosis of UTI in young children.

# STUDY DESIGN

The design is an interventional study in pre-continent children presenting to ambulatory care in whom a urine sample is deemed necessary by the treating physician, combined with a nested interview study conducted with general practitioners (GPs).

The interventional part of the study will focus on the feasibility of UC in general practice for diagnosing UTI in pre-continent children. This will be done by observing success rate, contamination rates and time-efficiency. The interview study will provide an insight in the general practitioner's thoughts on UC in general practice. Pre-existing thoughts will be recorded by using a questionnaire. An adapted version of this questionnaire will be used to record their thoughts on UC at the end of the study. Each questionnaire will be taken during a one-on-one interview by telephone between the investigator and every general practitioner (GP).

The study will run in general practices across Flanders. Recruitment to the study is expected to last 7 months, with each patient entering the study only once. Children and their parents/guardians will be approached for possible participation in the study by the GP. There is only one study visit.

Those who agree to participation via written informed consent will have demographics and clinical features recorded. The GP will then try to obtain a urine sample through UC in all

participating children, but only if it is not possible to collect urine spontaneously using the clean-catch method.

Treatment and other management decisions will be left to the treating physicians' discretion.

# PARTICIPANT IDENTIFICATION

## STUDY PARTICIPANTS

Pre-continent children aged between 3 months and 2 years presenting to a general practice with fever without an initial focus will be eligible.

## INCLUSION CRITERIA

GPs:

- GP in training or GP
- Solo working GP or working in a group practice
- General practice must be located in the province of Flanders
- They must see children weekly during their consultations
- It is allowed to include more than one GP of the same group practice

Children:

- Aged 3 months to 2 years
- Pre-continent
- Presenting with a fever without an initial focus found during anamnesis and clinical examination
- Parent or guardian is willing and able to give informed consent for participation

## EXCLUSION CRITERIA

There are no exclusion criteria for GPs.

The participant may not be included in this study if ANY of the following apply:

- Children under the age of 2 years who are continent
- Children who are clinically unstable or where ambulatory care is not possible because of the poor overall clinical condition
- When there are contra-indications for UC
    - Known urethral trauma
    - Acute pelvic fracture (symptoms may be a perineal hematoma or blood at the meatus)
- Recent genitourinary surgery
- Genital malformations, e.g. hypospadias
- Antibiotics taken in the previous 7 days

# STUDY PROCEDURES

## RECRUITMENT

General practitioners will be recruited via the Domus Medica newsletter and direct contact via email. We will select 10 GPs from those expressing interest using purposive sampling if possible, ensuring we include GPs of different ages, practice types and practice location (rural vs urban).

## TRAINING

Before the start of the study the participating GPs will be invited to a common training session.

The training session will consist of a theoretical and practical part, where they can see the materials for the first time and can exercise the procedure.

## SCREENING AND ELIGIBILITY ASSESSMENT

To inform parents/guardians of children (between 3 months and 2 years) about the study, there will be information sheets available in the waiting room of the practice, potentially handed out by a non-clinical staff member such as a receptionist. There will also be a poster displayed in the waiting room.

The GP will approach the parents during the consultation to check if they meet the inclusion criteria. If they are eligible, the GP will seek for informed consent.

## INFORMED CONSENT

As mentioned above, the GP will take the written informed consent from the parents/guardians.

Participant information sheets containing details of the background/rationale of the study, what it will involve for the child, the implications and constraints of the protocol, and any risks associated in participation, will be presented to the parents/guardians. In the informed consent it will be clearly documented that the parents/guardians have the right to withdraw their child from the study at any time and that this decision will have no implications on future treatment and care for the patient. It will be stated that this will not affect their legal rights and there is no necessity to give the reason for withdrawal, which can be done by email at any time after the study visit.

The parent/guardian will be given the opportunity to ask questions. Considering the nature of this study, i.e. trying to enhance diagnosis of UTI in general practice, the limited risks associated with UC and lack of impact on medical management, a limited time to consider the information seems warranted. We will obtain informed consent from at least one parent or guardian.

## STUDY VISIT

After obtaining the informed consent, the GP will record demographic information and clinical features of the child (sex, age, symptoms and who was accompanying the child).

Then the GP will proceed to obtain a urine sample of the child. First we will use the clean-catch method to collect the sample, when the GP fails to obtain urine spontaneously, he/she will perform UC as the collection method. A concrete step-by-step plan on how to perform UC in children can be found in Appendix A. The urine will be collected in a sterile container provided by the local laboratory, which then will be placed in laboratory collection bags. Finally these bags will be collected by the designated laboratory within 6 hours.

Following the procedure of UC, the GP will record if collecting a urine sample by UC was successful, if there were any problems during the procedure, the time it has taken, the laboratory results and the treatment.

After recording the above-mentioned information, no further follow-up of the child is necessary.

### INTERVIEW

Previous on the study the participating GPs will be answering a questionnaire to record their pre-existing thoughts on UC in general practice. Practically the questionnaire will be taken by telephone in advance of the training session.

At the end of the study the GPs will be answering an adapted version of the questionnaire, in this way a first qualitative evaluation of UC in general practice can be made.

Both questionnaires will be accompanied by a one-on-one interview by telephone between every GP and the investigator.

More detailed information on the questionnaires is listed below.

### DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

Each parent/guardian has the right to withdraw their child from the study at any time. In addition, the investigator may discontinue a child from the study at any time if the investigator considers it necessary for any reason, including ineligibility (either arising during the study or retrospectively having been overlooked at screening) or withdrawal of consent.

Withdrawal from the study will result in exclusion of the data for that child from analysis from that moment onwards. The reason for withdrawal (if given) will be recorded in the clinical report form.

If parents decide to withdraw their child's data from the study, they can inform the study team by email, which is included in the patient information sheet pack.

### DEFINITION OF END OF STUDY

The end of the study is the date of the last one-on-one interview between GP and investigator. The interviews take place after the 4 month-during period of including patients.

## IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL PROCEDURES

### URINARY CATHETERIZATION

Each GP will receive 5 UC kits, which will contain all the materials needed for the procedure (e.g. sterile gloves, gauze pads and swaps, sterile field, sterile lubricant gel, antiseptic, urethral catheter ...), this to lower the threshold and to make the collecting of materials more efficient. Sterile containers are available in every general practice, provided by the local laboratory.

Next the GP will perform UC by using a prepared UC kit. Step-by-step instructions on how to perform UC in boys and girls are listed in Appendix A. Each GP will receive a print out version of the step-by-step instructions on the training session, besides an overview of the materials and different steps, there will be a link to an instruction video as well.

The collected urine sample in the sterile container will be linked to a laboratory request.

### URINE TESTS
The collected sample will be used for urine culture and sediment, which is the reference standard.

Urine samples will be obtained on the day of study inclusion, using UC or the clean-catch method (if the children start urinating spontaneously). Samples will be collected by the central laboratory from the practices. Ideally samples are tested within 2 hours; when this is not feasible, samples will be stored in a refrigerator at 4°C. All urine tests will be conducted in the laboratory by trained personnel.

### QUESTIONNAIRE PRE
The first questionnaire will be taken by telephone in advance of the training session before the theoretical explanation and background is explained. This to get a good representation of GP's pre-existing thoughts on UC in general practice and to minimize the risk of bias. The questionnaire will exist of 10 open questions to get feedback in the GP's own words.

A Dutch version of the questionnaire can be found in Appendix B.

### QUESTIONNAIRE POST
After the 7 month-during period for including patients, a second questionnaire will be taken by telephone as a one-on-one interview so the GPs will be able to express their thoughts on UC in general practice. This questionnaire will contain adapted versions of the questions in questionnaire PRE and some extra questions, this way we will get to know if the study and practicing UC had an impact on their opinions.

A detailed Dutch version is available in Appendix C.

## STATISTICS AND ANALYSIS

### DESCRIPTION OF STATISTICAL METHODS
Statistical methods for this Proof of Concept study will focus on the practical evaluation of UC in general practice. Because this is small study, the use of statistics will be limited. We will use descriptive statistics to become success rates, contamination rates and time-efficiency. Interviews will be analyzed thematically to identify common themes and patterns.

### SAMPLE SIZE
Because this is a Proof of Concept study for UC in children in general practice, the study will not include a large number of participants. It will be a first practical evaluation of UC done by GPs and the study will be a stepping stone to larger studies where sufficient power is needed to prove the role of UC in general practice. Therefore we start with a small group of ten GPs, which each will try to include as much children as possible. We will provide 5 kits to every GP, so we aim to include five participants per GP and a minimum total 50 participants.

### ANALYSIS OF OUTCOME MEASURES
Success rate

The primary outcome of the study is success rate of UC performed by GPs. We want to record in how many of the patients, where GPs tried to perform UC, it was possible to effectively obtain a urine sample.

Contamination rate

One of the secondary outcomes of this study is contamination rate, we will use a proportion to analyze how many of the by UC obtained urine samples are contaminated.

Time efficiency

In general practice time-management is very important, therefore a possible threshold to perform UC as a GP is the time it takes to obtain a urine sample. We will record how many minutes it will take starting from the moment the doctor opens the UC kit to the moment the doctor closes the obtained urine sample. We will calculate the mean and median to analyze time efficiency.

Interview study

The qualitative part of the study where we evaluate the pre- and post-study opinions on the role of UC in general practice is based on questionnaires. We will use a theory-driven process that includes coding the data and categorizing the codes into concepts.

# DATA MANAGEMENT

## ACCESS TO DATA

Direct access will be granted to authorized representatives from the host institution for monitoring and/or audit of the study to ensure compliance with regulations.

## DATA RECORDING AND RECORD KEEPING

All study data will be recorded digitally into a password protected electronic database RedCap, hosted by the investigators and after study closure at the Academic Centre for General Practice (ACHG), University of Leuven. Paper files will be kept in a locked filing cabinet during data collection and at the ACHG after study closure. The participants will be identified with a study specific participants number and/or code in any database. The name and any other identifying detail will not be included in any study data electronic file. The identifier will be stored separately and securely on a password-protected computer at the ACHG.

# QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, Good Clinical Practice, relevant regulations and standard operating procedures.

# ETHICAL AND REGULATORY CONSIDERATIONS

## DECLARATION OF HELSINKI

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

## GUIDELINES FOR GOOD CLINICAL PRACTICE

The investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

### APPROVALS
The protocol, informed consent forms, participant information sheets, information cards for GPs and any proposed advertising materials will be submitted to an appropriate Research Ethics Committee for written approval.

The investigator will submit and, where necessary, obtain approval from the above party for all substantial amendments to the original approved documents.

### REPORTING
An End of Study notification will be submitted to the Ethical Research Committee. A final report will be submitted to the KU Leuven.

### PARTICIPANT CONFIDENTIALITY
The study staff will pseudonymize the participants' data. The participants will be identified only by a participant ID number on all study documents and any electronic databases, with the exception of the clinical report form. All documents will be stored securely and only accessible by study staff and authorized personnel. The study will comply with the Privacy Act.

### OTHER ETHICAL CONSIDERATIONS
The study will recruit pre-continent children aged between 3 months and 2 years. Parents/guardians will be asked for consent after being fully informed about the goal and procedures of the study. Limited time will be provided to consider participation due to the need of obtaining a reliable urine sample in acutely ill children, the limited risks associated with UC and the lack of impact on medical management. UC is a safe, effective and frequently used technique. UC can cause a little discomfort during a short period of time. We have attempted to reduce discomfort by using lubricant and by performing this procedure while the parent/guardian can hold the child and put them at ease. There is a minimal risk on complications (hematuria, iatrogenic infections), but it has been scientifically proven that the benefit of obtaining a urine sample via urethral catheterization far outweighs the inconveniences and risks of this procedure.

## FINANCE AND INSURANCE

### FUNDING
The study is funded by the KU Leuven.

### INSURANCE
The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Vanbreda Risk and Benefits NV, insurance number 299.053.700).

### PUBLICATION POLICY
The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the KU Leuven. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

# ADVERSE EVENT REPORTING

## DEFINITIONS

### ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

### ADVERSE REACTION (AR)

An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

### SERIOUS ADVERSE EVENT (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Death
- A life-threatening[a] experience
- In-patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

*[a] The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.*

## ADVERSE EVENTS THAT DO NOT REQUIRE REPORTING

In general, the following should <u>not be reported as AEs:</u>

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

The following events <u>not to be considered as SAEs</u> are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

## RECORDING AND REPORTING OF ADVERSE EVENTS

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE page, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the study , adverses
- outcome

### ASSESSMENT

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:**
    - Severity must be evaluated by an Investigator according to the following definitions:
        - *Mild* – no or transient symptoms, no interference with the subject's daily activities
        - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
        - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**
    - *None* – An AE which is not related to the study-related interventions
    - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
    - *Possible* – An AE which might be due to the study-related interventions. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
    - *Probable* - An AE which might be due to the study-related intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
    - *Definitely* – An AE which is known as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

### TIMELINES FOR REPORTING

After informed consent has been obtained and after initiation of study-related interventions:

- All AEs and SAEs causally related to a study-related intervention will be reported until last (follow-up) visit.

All SAEs as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by Trial identification.

SAE details will be reported by the Investigator to the Sponsor:

- By completing a paper SAE form and sending it to the following address:
  - Mail: ann.vandenbruel@kuleuven.be

If an authorised Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

### FOLLOW-UP

The Investigator must record follow-up information by updating the medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

**SAEs after the end of the trial:** If the Investigator becomes aware of an SAE with suspected causal relationship to the study-related interventions after the subject has ended the trial, the Investigator should report this SAE within the same timelines as for SAEs during the trial.

### DEATH

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event). The sponsor will notify all deaths, as soon as possible after becoming aware, to the Central EC and the EC of the concerned site and provide additional information if requested.

## REPORTING REQUIREMENTS TO ETHICS COMMITTEE'S (EC'S)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and based on applicable legislation.

### ANNUAL REPORTING

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's containing an overview of all SARs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

### OVERVIEW REPORTING REQUIREMENTS

| | WHAT | HOW | TO | TIMELINES |
|---|---|---|---|---|
| Investigator | AE | AE form | sponsor | as defined in protocol |
| | SAE | SAE form | sponsor | Immediately (within 24 hours of becoming aware of the event)<br>Exceptions: as defined in protocol |
| | death | SAE form | sponsor | asap |
| Sponsor | death | SAE form + narrative | Ethics Committees | asap |
| | Annual Progress Report | APR template | Ethics Committees | annually |

# REFERENCES


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2. Hadjipanayis A, Grossman Z, Torso S Del, Van Esso D, Dornbusch HJ, Mazur A, et al. Current primary care management of children aged 1-36 months with urinary tract infections in Europe: Large scale survey of paediatric practice. Arch Dis Child. 2015;100(4):341–7.
3. Stein R, Dogan HS, Hoebeke P, Kocˇvara R, Nijman RJM, Radmayr C, et al. Urinary Tract Infections in Children: EAU/ESPU Guidelines. Eur Urol. 2015;62:546–58.

# APPENDIX A STEP-BY-STEP INSTRUCTIONS FOR URETHRAL CATHETERIZATION

Step-by-step instructions for UC in girls:

1. Ask the parent to hold the legs in the supine and frog leg position
2. Use alcohol gel to disinfects your hands
3. Wash the genitalia with water and soap
4. Open the catheterization set and bring together all the materials on the sterile field (lubricant gel and catheter)
5. Wet the gauze swabs with Chloorhexidine
6. Open the sterile container for urine collection
7. Put on sterile gloves
8. Apply sterile lubricant gel on the tip of the catheter
9. Lift with your nondominant hand the labia majora anteriorly, laterally and cephalad to expose the urethra
10. With your dominant hand disinfect the genitalia carefully, swab from front to back and start at the farthest side (three times)
11. Take the catheter out of the sterile field with your dominant hand, hold it between thumb and index finger
12. Place the catheter in the meatus advance carefully until urine returns
13. Try to collect the midstream part in the sterile container
14. Remove catheter

Step-by-step instructions for UC in boys:

1. Ask the parent to hold the legs in the supine and frog leg position
2. Use alcohol gel to disinfects your hands
3. Wash the genitalia with water and soap
4. Open the catheterization set and bring together all the materials on the sterile field (lubricant gel and catheter)
5. Wet the gauze swabs with Chloorhexidine
6. Open the sterile container for urine collection
7. Put on sterile gloves
8. Apply sterile lubricant gel on the tip of the catheter
9. Retract the foreskin of the glans gently with your nondominant hand to permit complete visualization of the urethral meatus if the boy is uncircumcised
10. Hold the penis perpendicular to the lower abdomen with gentle traction
11. With your dominant hand disinfect the genitalia carefully, start at the meatus and go from central to peripheral (three times)
12. Take the catheter out of the sterile field with your dominant hand, hold it between thumb and index finger
13. Place the catheter in the meatus advance carefully until urine returns, when encountering resistance bring the penis horizontally
14. Try to collect the midstream part in the sterile container
15. Remove catheter