PROTOCOL FOR NON-EXEMPT RESEARCH INVOLVING HUMAN SUBJECTS

Title:	**E**PIC: **E**ffect of **P**ovidone **I**odine periurethral **C**leansing on level of contamination with clean catch: A randomized control trial
IRB #:	FWH20190009H

Principal Investigator (PI)	Rank	Branch	AD/DoD Civ/ Ctr/Civilian	Dept/Base	Phone #	E-mail
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The research relevance of this protocol focuses on:					
☒	**Diagnosis**	☐	**Treatment**	☐	**Medical Utilization/Managed Care**
☐	**Prevention**	☐	**Medical Readiness**	☒	**Other:** New method of urine collection in children

Does the research fall under the purview of any other departments or committees?	No

1. LOCATION AND SPONSOR

Collaborating Facilities:

99MDG/Mike O'Callaghan Military Medical Center

AF Sites Seeking Regional IRB:

Jill Clark, (702) 653-3298, jill.m.clark15.ctr@mail.mil

Study Sponsors: None

2. RESEARCH PLAN

Purpose of Study:

The primary aim of this study is to see if the use of an antiseptic preparation (povidone iodine) versus cold normal saline, will decrease rates of urine contamination during the non-invasive Quick Wee (QW) collection of pediatric urine.

Hypotheses, Research Questions, or Objectives:

To evaluate two different cleansing solutions in controlling urine contamination.

Significance

If the use of antiseptic preparation decreases the level of contamination in this study then it would provide an effective and reliable clean catch method that staff could utilize prior to electing for catheterization or suprapubic aspiration.

Military Relevance:

Having a noninvasive Quick Wee method with a high 5 minute void success rate; patient wait times in the emergency department will decrease, and parents will be happier with avoiding invasive measures. This improves patient safety, and provides the clinician with another method for collecting urine. In the Air Force's move towards a culture of safety, and zero harm; further evaluation into this novel technique's reliability will support our goals provided rates of urine contamination can be minimized. The importance of researching noninvasive methods with low levels of contamination is that it may prevent further invasive methods from being used. For example if a child's urine specimen from clean catch is contaminated the next step would be to get the sample via catheterization, a method that is traumatic to child, parent and sometimes staff. If research shows that urogenital prep with iodine decreases level of contamination in the urine then it provides an acceptable method of urine clean catch collection.

Background and Review of Literature:

Urinary tract infections (UTI) are common acute illnesses among pediatric patients, accounting for 5-7% of emergency department visits in the under two-year-old population [1]. However, obtaining urine samples from the precontinent patient can be difficult. There is an ongoing debate regarding which noninvasive method for urine specimen collection is best for this population. The main argument against clean catch is the high rate of contamination compared to invasive collection and reliability.

There are many methods of noninvasive urine collection. These methods are preferred as they are fairly well tolerated by patients, less distressing to parents, cost effective, and require less technical expertise. In the past; these methods have been dismissed due to their high rates of contamination, time to void and also effectiveness. The National Institute of Health and Clinical Excellence (NICE, UK) recommends a clean-catch urine (CCU) be the first attempt at obtaining a urine specimen from children suspected of having UTI [2]. This means placing the urine specimen collection container into the urine mid-stream once the child has begun to void to avoid contamination. Conversely, the American Academy of Pediatrics recommends clean

catch urine for screening and a catheter specimen urine collection or suprapubic aspiration for definitive diagnosis [3]. Both of these invasive techniques produce quick urine samples with low rates of contamination; however they can be painful and distressing to both the patient and parent.

The Quick-Wee method for noninvasive urine collection has been evaluated in a one randomized controlled trial and has been shown to significantly increase the five minute voiding success rate for CC urine collection; 31%, n= 174. However a past study demonstrated contamination rate of 27%, n=174. No study has directly evaluated the use of antiseptic solution in the evaluation of the QW rate of contamination in pediatric patients. The purpose of this study is to see whether the use of povidone iodine swabs prior to the QW method will decrease the rate of contamination. A decrease of the rate of contamination would strengthen the validity of this simple CCU method. Also using the this method for the collection method in both the experimental and control groups will further evaluated the five min void success rate.

We chose to use iodine as our prepping agent because it is currently the standard cleaning solution used for adult and pediatric patients. It is readily available, inexpensive and has been shown to be less caustic then other prepping agents.

Bibliography:

1. Shaw, K. N., Gorelick, M., McGowan, K. L., Yakscoe, N. M., & Schwartz, J. S. (1998). Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics*, *102*(2), e16-e16.
2. Baumer, J. H., & Jones, R. W. A. (2007). Urinary tract infection in children, National Institute for Health and Clinical Excellence. *Archives of Disease in Childhood-Education and Practice*, *92*(6), 189-192.
3. Representatives, L. (1999). Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics*, *103*(4), 843-52.

3. RESEARCH DESIGN AND METHODS

Research Design and Methods:

Male and Female DoD beneficiaries, aged one month (28 days) to 12 months (365 days), meeting the inclusion/exclusion criteria will be offered an opportunity to participate. Each child will already be scheduled for a standard of care urinalysis collection procedure through their pediatric PCM. They will be recruited from the clinics located at the 99MDG through direct contact with the infant's parents. All of the below items are research-related unless marked as 'standard of care':

The study will be a non-blinded randomized controlled trial with parallel assignment of groups, taking place in the pediatric and emergency departments. The subject's parents will be asked if the patient has had an allergic reaction to iodine in the past prior to being placed in experimental group and if they have had a reaction in the past they will be placed in the normal saline group instead. Additionally, if the patient develops a reaction to iodine during testing then they will have the region cleansed with normal saline, will be evaluated by the medical staff performing the test, then the urine and subject's data will be disposed of and excluded from the study. The experimental group will have their periurethral region cleansed with povidone iodine solution while the control group will be prepped with cold (2^{o}C) normal saline. Both groups will have the urine collection performed utilizing the QW method (see attached flow chart). If a sample is not collected within five minutes with the QW method it will be documented as a failure and the child will be referred back to their pediatric PCM and removed from the study. Urine collection will occur at the hospital.

Utilizing sequentially numbered opaque sealed envelopes (SNOSE), children will be randomly assigned to one of the two treatment groups. The envelopes will contain plastic forceps, gauze, and a 3x5 index card listing the group the child has been assigned, i.e., iodine or normal saline, as well as child's ID number; For the experimental group there will be a package of iodine swabs and the control will have a normal saline flush. Also contained within the envelope will be the Participant Data Sheet to provide an easy way to track the urine collection process for the study..

Children will then have their periurethral region gently cleansed for ten seconds with one of the previously discussed solutions. The procedure requires cold saline (approximately 2°C) soaked gauze to be applied in a circular motion over the bare suprapubic region of the child continuously for five minutes. The saline will come in the form of sterile saline flushes kept in a cooler of ice in the departments were the study is being conducted.

If the child voids within five minutes the time in seconds will be recorded on the provided worksheet. Also whether or not the urine was successfully "caught' in the specimen cup will be documented. Whether or not the sample was contaminated by lab standards will also be recorded on the data sheet once the results are available.

At the conclusion of the child's participation, the parents will be asked to complete a Satisfaction Survey asking their overall satisfaction with the collection method utilized.

a. Interventions and Observations:

The primary outcome of this study is to evaluate whether there is an improvement in the rate of urine contamination with iodine solution over normal saline prior to the QW. The secondary outcome will be the QW's rate of success in providing a CCU in five minutes.

b. Setting:

This study will be conducted at the 99MDG at Nellis AFB. Children will be recruited from the emergency department as well as the pediatric clinic through parental permission and consent. Research Staff will enroll children through parental authorization, based on the child's age, and if a standard of care urinalysis will be needed during their course of treatment, based on the determination of the child's attending physician. If a urinalysis is not needed as a course of treatment for the infant, the child will not be accepted for the study.

c. Date(s):

11 January 2019 – 31 May 2019

d. Subjects:

The sample population for this study are DoD beneficiary children from 28 days of age to 12 months requiring a standard of care urinalysis procedure as a course of treatment. They will be patients enrolled at 99MDG for evaluation and treatment. Children will be recruited from the pediatric clinic as well as the emergency department through parental permission and consent.

e. Inclusion/Exclusion Criteria:

Inclusion Criteria	• DoD children aged one month (28 days) to 12 months (365 days) • if the child was born less than 36 weeks gestation, age will be corrected • Precontinent (meaning that the child is unable to void on command) • Treating clinician has determined that the child requires urine sample collection for course of treatment.
Exclusion Criteria	• Children that are outside of the age range discussed in the inclusion criteria (less than one month (28 days) and older than 12 months (365 days)). • If the treating clinician has determined that there is a need for immediate treatment and urine sample collection via invasive method, any type of anatomical or neurologic condition that will affect the ability to void or sensation of the suprapubic area. Children with past hypersensitivity reactions to iodine swabs.

f. Source of Research Material:

Will you be using private information in this study?	☒Yes
If Yes	☒protected health information (PHI) held by a covered entity

Use of identifiers with private information

Identifiers to be Used?	**Column A** Looked at by research team	**Column B** Recorded on enrollment log, subject list, or key list	**Column C** Recorded on data collection tool (survey, spreadsheet, etc.)	**Column D** Recorded on specimen containers	**Column E** Shared w/ others not on research team	**Column F** Stored after study ended
Names	☒	☒	☐	☒	☐	☐
Study codes linked to individuals' identities using a key only accessible by the researcher		☒	☒	☐	☐	☐
Dates (except year)	☒	☒	☐	☒	☐	☐
Phone/Fax Numbers	☒	☐	☐	☐	☐	☐
DoD ID# & FMP code	☒	☒	☐	☒	☐	☐

Coding Plan?	
Describe the method that will be used	Each participant will be assigned a patient identifier starting with either A or B to

to create and assign unique study codes to data.	show which group they were a member of and number 01-60 following the letter.
Describe the method that will be used to create and assign unique study codes to specimens.	Urine specimens will be associated with the child's DoD ID# and FMP code for the initial results from the hospital laboratory and then the microscopy results will be put into the work book and the original results will be shredded. On the work book the results will assigned to the child's study code.
What is the format of the key?	☒Electronic
Who will have access to the key?	Research Coordinators and Investigators
Where will the key be stored and how will it be protected?	Location(s): All research data will be kept separately from the Master Key of coded, identifiable PHI/PII in an electronic database, which will be encrypted, double password protected and the access will be restricted. At the conclusion of the study, the research data will be de-identified prior to review and analysis. Confidentiality measures: The research data will be coded to mask the identity of the child. The code will be retained until the conclusion of the research study. Once a Final Report has been approved by the IRB, all the paper records will be stored and destroyed in accordance with the Long Term Storage Plan. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. At the end of all data mergers, or no later than at the closure of the study, all identifiable patient information will be destroyed based on AFI 33-332, "The Air Force Privacy and Civil Liberties Program" and the National Institute of Standards and Technology Special Publication (NIST SP 800-88) for the approved methods to destroy PII.

Source of Research Material per Participant (Procedures)	**# Routine Care**	**# Research Driven**	**# Total Procedures**
Urine specimen	1	0	1
Participant Data Sheet completed by research staff	0	1	1
Satisfaction survey (Parent)	0	1	1

"All specimens kept at 99MDG will be handled and disposed of in accordance with federal regulations."

g. Instrumentation: N/A

4. HUMAN SUBJECT PROTECTION

Recruitment and Consent Processes:

All potentially eligible childrens' parents will be approached to have their child participate. Primary Care Manager (PCM) referrals, with the patients' parents oral or written authorization, and posted advertisements will be utilized for recruiting children to the study. Some children may be patients of the PI or AI, however, they will have another study staff recruit the children through their parents to prevent any misconception of coercion or undue influence. When a potential child is identified by the treating PCM, their parent(s) will either be provided a contact number to the Research Staff, the Research Staff will be given the potential subjects contact information by the PCM with the parent's oral or written authorization, or the Research Staff will speak with the child's parent(s) directly, if contacted by the parent.

Consent Processes:

Parental Informed Consent (ICD) and HIPAA Authorization (HIPAA) will be sought in advance from each prospective child's parent(s) and appropriately documented in accordance with 32 CFR 219.117. Potential childrens' parents will be notified about the study either through posted advertisements, verbally through their child's primary care manager, or upon check in at the clinic and will be given the opportunity to consent for the child by one of the referred study coordinators. The study coordinator will provide a written copy of the Parental Informed Consent Document and HIPAA Authorization. The potential child's parents may decline to consent for the child without prejudice. At the parent's discretion, they may take the ICD and HIPAA home to discuss further prior to making a decision. If the parent consents to having their child enrolled in the study, a copy of the ICD will be given to them. Each parent will be asked to allow us to include their child's de-identified research data into the "Mike O'Callaghan Military Medical Center General Research Data Repository (FWH20180064H)" for future research.

Recruiting Service Members	Will you be recruiting service members in a group setting?	☐Yes	☒No

Participation Compensation:

Children and parents will not be paid for participation in this study.

Assent Process:

Parent consent will be acquired via the written consent forms prior to the initiation of any research activities.

Benefits:

There may be decreased levels of urine contamination in either the saline or the iodine prep group's urine sample. If so, this will give a child's treatment team more reliable test results and decrease the need for more invasive urine testing. Additionally the normal saline preparation may be effective at decreasing the level of contamination as the iodine, this is the benefit of using normal saline for a preparation and comparing it to the iodine.

Risks:

Procedure is safe and the only possible negative outcome could be skin irritation from the iodine prep group. There are risks that urine sample may show that there was growth of bacteria on culture in which event the parents will be contacted by the PI or AI and made aware of these results and will be advised to follow up with their pediatrician. There is a possibility that the child has an allergic reaction to the iodine swab. If this occurs, the child will be referred to their pediatric PCM. The urine sample collected during the QW procedure will still be used for the study. There may be a risk of inadvertent breach of confidentiality.

Costs: None

Safeguards for Protecting Information:

Parental Informed Consent and HIPAA authorization will be sought in advance of any screening and study-related procedures for each prospective child participant and appropriately documented in accordance with 32 CFR 219.117. Parents of potential children will be notified about the study either through posted advertisements or through their healthcare provider and parents will be given the opportunity to be consented by one of the referred study coordinators. The study coordinator will provide a written copy of the Informed Consent Document (ICD) to the parent. The parent may decline to consent for their child without prejudice. At the parent's discretion, they may take the ICD home to discuss further with family members or another physician, prior to making a decision. If they decide they are interested in their child participating in the study, they can contact the research department. If the parent consents, a copy of the signed ICD and HIPAA Authorization Document will be given to the parent. Parents who cannot provide Informed Consent on behalf of their child, then the child will not be allowed to participate in the study. No Legally Authorized Representatives (LAR) will be utilized. Each parent will be asked to place their child's de-identified research data into the "Mike O'Callaghan Military Medical Center General Research Data Repository" (FWH20180064H) for future research. If the parent does not give their authorization, then the child's de-identified research data will be destroyed no later than 3 years following the closure of the study.

Data and Specimen Storage Plan

How will coded or identifiable data/specimens be stored?

☒	Paper data, including completed consent forms	The research consents and HIPAA Authorization Documents will be stored in a locked cabinet in a locked room with restricted access.
☒	Electronic data	Medical records will not be annotated to reflect the child's participation in a research study since the child will not receive an invasive research intervention or procedure. All coded, de-identified research data will be electronically stored separately from the Master Key of identifiable patient demographics and PHI/PII.
☒	Specimens	Urine samples will be disposed of by the lab after analysis is complete. Results will be acquired through CHCS using the child's DoD ID# and name. DoD ID# will be used initially for urinalysis results tracking and then Study code IDs will be used for de-identified research data
☒	Long-term storage (following completion of the study and inactivation of IRB approval)	The research data will be coded and any links to identifiable data will be destroyed (an approved shredding bin) as soon as possible or no later than at the closure of the study, with the exception of those parents that consented to place their child's de-identified research data into the "Mike O'Callaghan Military Medical Center General Research Data Repository" (FWH20180064H) for future research. The anonymized

		research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. All de-identified research data will be maintained for 3 years following study closure.

Safeguards for Protecting Subjects Relative to Reasonably Expected Risks:
The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the 59 MDW IRB and over sight staff for confirmation of the study data. If at any time the parent reports a side effect being experienced by their child, they will be referred to one of the Investigators for care or to the child's pediatric PCM.

Categories of subjects	☒Children (17 yrs or less), includes viable neonates (28 days of age to 12 months)

Clinical Care:
All children will receive standard of care regardless of inclusion into this study. If at any time a child experiences any injury or adverse effects, appropriate clinical care will be given or the child will be referred to appropriate provider. If a urine sample should be abnormal the PI or AI will follow up with the child's parents and ensure they either follow up with their primary care provider or report to the emergency department, if symptomatic.

Injury Compensation: N/A

Data Safety Monitoring	☒N/A – none of the situations listed above apply

5. ALTERNATIVES

Alternatives:
The alternatives for QW urine collection are urine specimen collection by using the bag specimen collection method or the invasive straight catheterization or suprapubic aspiration. The alternative to using an iodine cleansing solution is to use a normal saline solution. The parents also have the authority to deny their child's participation in the study.

6. DATA ANALYSIS

Data Analysis:
Primary analysis will be performed by intent-to-treat including all randomized children, where primary outcome data are available, consistent with the CONSORT guidelines for intention to treat analysis. The primary outcome measure is a binary yes/no outcome of detection of microbial markers to determine level of contamination. The absolute difference between the two groups will be reported so that the percentage of contamination samples, together with the 95% CI for the differences of percentages, and calculate p values using a chi squared test. A p value of <0.05 will be considered significant. For the secondary outcome there will also be a measure of binary yes/no outcome of voiding urine within 5 minutes. The rate of successful voiding within 5 min will be described for each group with percentages and 95% CI. The p value will be estimated using chi squared test for categorical variables and t-test or Wilcoxon's rank sum tests for continuous variables. Additionally we will also be evaluating patient's gender, and age in months for comparative data analysis to help strengthen the study's statistical design outcomes.

Outcome Measures:
Level of urine contamination (binary yes or no), if there was a sample collected in 5 minutes (binary yes or no), and time to void with a 300 second cap are the two outcome measures being evaluated in this study.

Sample Size Estimation/Power Analysis:
This is a pilot study and will have a relativity low sample of 60 subjects.

Statistical Analysis:
Data analysis will be conducted by Baylor University statistics department (Dr. Jack Tubbs)

Number of Subjects:	# Planned to Enroll	# Enrolled	# Planned to Complete Study	TOTAL

Number of Subjects at 99 MDG	60	0	60	60

7. STUDY DURATION

Duration of Study:
Approximate duration of the study: four months

8. LOCAL AND EXTERNAL SUPPORT SERVICES

Local and External Support Services: None	
Describe the plan for training/informing clinical personnel about the study.	Who will you train? ☒Other: Nursing staff who will perform the QW and urine collection and will be instructed when to use an iodine swab or saline flush to cleanse the periurethral area. When will you provide the training? ☒Prior to the first subject being enrolled. How will you provide the training? ☒In person

9. INTRAMURAL (GME) AND EXTRAMURAL FUNDING SUPPORT

Intramural (GME) and Extramural Funding Support: None

10. DRUGS, BIOLOGICS, DIETARY SUPPLEMENTS, AND MEDICAL DEVICES

Is this research an "applicable clinical trial" which must be registered on ClinicalTrials.gov? ☒No

Use of a placebo in place of standard therapy:		
Is a placebo being used in place of standard therapy?	☒No	☐Yes

11. MEDICAL RESEARCH AREA

☒Emergency medicine	☒Pediatrics

12. ATTACHMENTS

1. Form A, Signature Sheet
2. Form A-2, Study Personnel Listing
3. Form D, Informed Consent Document
4. E-1 Parental HIPAA Authorization Form
5. H23 Template, Research Involving Children Form
6. Recruitment Flyer
7. Participant Data Sheet
8. Lab Letter of Support
9. Flow Chart QW
10. Application Checklist