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A 15-year retrospective review of urodynamic studies in children at Red Cross War Memorial Children's Hospital, Cape town, South Africa

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Declaration

I, Thembisile Dintle Mosalakatane, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background:

Despite the undeniable diagnostic benefits of urodynamic studies (UDS), their adoption into clinical practice in Africa has been slow. This study aimed to review the use of invasive UDS in children at a tertiary paediatric hospital in South Africa.

Methods:

A retrospective analysis of 1108 UDS was conducted. Patient demographic characteristics, primary diagnosis, indication and urodynamic outcomes were reviewed. Presence of urodynamic high-risk features were documented, and a comparison was made between the first study and follow-up study.

Results:

This study revealed increasing trends in the use of UDS from 2015. Referrals were from Urology (37.7%), Spinal defects clinic (34.4%), Nephrology (20.8%) and other departments (7.0%). The most common reason for referral was review of medical treatment (36.5%). Spinal dysraphism (58.3%) accounted for the majority of conditions seen. Majority (59.1%) of the patients were receiving more than one type of bladder treatment at the time of their first study, with clean intermittent catheterisation (46.5%) being the most common form of bladder management. 97.5% of studies were performed using transurethral bladder catheterization. Urodynamic diagnosis was neurogenic in 74.0%, anatomical (12.2%), functional (8.8%) and normal (5.0%). There was statistically significant improvement in bladder compliance, detrusor leak point pressure and detrusor sphincter dyssynergia between the first study and a subsequent study following therapeutic intervention.

Conclusion:

The unique ability of UDS to demonstrate changes in detrusor pressures, which is a common reason for therapy failure, makes UDS an invaluable tool in the diagnosis and management of children with lower urinary tract dysfunction.

Abbreviations

CIC	Clean Intermittent Catheterisation
DSD	Detrusor Sphincter Dyssynergia
EAU	European Association of Urology
EBC	Expected Bladder Capacity
EFP	End-Fill Detrusor Pressure
ESPU	European Society for Paediatric Urology
ESKD	End Stage Kidney Disease
ICCS	International Children's Continence Society
IQR	Interquartile Range
KUB	Kidney-Ureter-Bladder
DLPP	Detrusor Leak Point Pressure
LUTD	Lower Urinary Tract Dysfunction
NDO	Neurogenic Detrusor Overactivity
NLUTD	Neurogenic Lower Urinary Tract Dysfunction
NNLUTD	Non-Neurogenic Lower Urinary Tract Dysfunction
PUV	Posterior Urethral Valves
RCWMCH	Red Cross War Memorial Children's Hospital
SPSS	Statistical Package for Social Sciences
TUC	Transurethral Catheterisation
UDS	Urodynamic Study
UTI	Urinary Tract Infection
VCUG	Voiding Cystourethrogram
VUDS	Video Urodynamic Study
VUR	Vesicourethral Reflux

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1.0 Introduction

Lower urinary tract dysfunction (LUTD) is a common problem causing a major social and psychological burden to both children and their families. If left untreated, some cases of LUTD such as anatomic, neurogenic or severe dysfunctional voiding, may cause irreversible kidney damage. The goal of treatment is therefore aimed at protecting the kidneys and ensuring urinary continence, with direct positive effects for the child's quality of life [1]. The treatment of LUTD greatly depends upon establishing the correct diagnosis. The complex and multifactorial nature of LUTD at times makes it difficult to diagnose and treat. Traditionally, the evaluation of a child with LUTD includes a history, physical examination, bladder and stool diaries, kidney-ureter-bladder (KUB) ultrasonography and voiding cystourethrogram (VCUG). Unfortunately, there is a sizable proportion of patients in whom conventional approaches fail to provide an explanation of their symptoms.

Urodynamic study (UDS) is an emerging modality in paediatric practice that has been used to identify other lower urinary tract (LUT) pathologies where conventional modalities have failed to establish a diagnosis. The major benefit of UDS is its ability to assess the mechanical function of the bladder, sphincter and urethra [2]. These tests are either invasive or non-invasive. Invasive UDS has an advantage over other modalities as the only investigation that is able to assess detrusor pressures during bladder filling and voiding phases. A video urodynamic study (VUDS) is an all-in-one invasive UDS which combines the standard UDS with a VCUG. When VUDS is performed, information on both mechanical function and anatomy of the LUT can be obtained [2, 3]. There is compelling data that support its use in patients with neurogenic lower urinary tract dysfunction (NLUTD) [4, 5]. The International Children's Continence Society (ICCS) now recommends UDS (preferentially VUDS) for all children with spinal dysraphism and those with suspected neurogenic bladder from other causes [4]. Several institutions have now begun to adopt universal rather than risk stratified UDS protocols for children with spinal dysraphism [6].

Invasive UDS is not without its own inherent problems. It involves bladder catheterization, which may cause discomfort and anxiety in a child. Many authors do not recommend its routine use in assessing children with non-neurogenic lower urinary tract dysfunction (NNLUTD) [7, 8]. They argue that UDS does not generally change the management and

treatment in these patients, as in most cases a detailed voiding history and physical examination is usually sufficient for a correct diagnosis [7, 8]. It is therefore, suggested that, in these types of patients, UDS be reserved for children who are failing standard therapy or where conventional investigations have failed to provide answers for their symptoms [9]. Some authors support its use in the evaluation of children with recurrent urinary tract infections (UTI) associated with history of voiding dysfunction (frequency, urgency and incontinence) [10, 11].

As the role and demand of UDS in both paediatric urology and nephrology increases, several studies have exposed gaps in the literature relating to method of bladder catheterisation (transurethral vs suprapubic) and type of anaesthesia (local vs general) when performing the study, and definition of high-risk features for kidney damage [2, 12-14]. There is also lack of data in the use of UDS in the African context, and current knowledge on urodynamic investigations in the African paediatric population is mainly based on studies done in Europe, North America and Asia. This study was undertaken to describe the 15-year experience with the use of invasive urodynamic studies conducted at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South Africa during the period September 2005 to September 2020.

The specific objectives for this study are:

1. To identify the common indications for urodynamic studies at RCWMCH.
2. To determine the prevalence and aetiology of both non-neurogenic and neurogenic lower urinary tract dysfunction in children undergoing urodynamics investigation at RCWMCH.
3. To determine the proportion of patients with active bladder interventions such as clean intermittent catheterization (CIC), antimuscarinic/ anticholinergic medication, intravesical Botox injection, Deflux®(Hyaluronic acid/Dextranome)/STING (subureteral Teflon injection) procedure, ureteral reimplantation and bladder augmentation.
4. To determine the proportion of patients with high-risk features [low bladder compliance, detrusor leak point pressure (DLPP) ≥30 cm H_2O, presence of neurogenic detrusor overactivity (NDO), presence of detrusor sphincter dyssynergia (DSD)] for upper urinary tract damage.

2.0 Materials and methods

2.1 Study site

The RCWMCH Urodynamics & Manometric Unit was established in September 2005. Initially the unit provided services mainly to the Spinal Defect Clinic. The unit has expanded over the years to include investigation of children with LUTD due to causes other than spinal dysraphism. Services offered include Uroflowmetry, Urodynamics, Video Urodynamics, Ambulatory Urodynamics, pH Impedance Studies, and Anorectal Manometry. Urodynamic testing is performed by a trained medical technologist, who has undergone training in urodynamics. Until the year 2016, the studies were performed using the Medtronic Urodynamic Measurement System. The urodynamic studies are now performed using the Nexam Pro Urodynamic System. It is the standard practice of the hospital to perform UDS following the ICCS good urodynamic practices [12]. All studies are performed and interpreted by a urodynamic technologist and reviewed by an experienced urologist. Complex cases or inconclusive studies are usually discussed during weekly combined (radiology, urology and nephrology) meetings.

2.2 Study population

This work covers a fifteen-year period from September 2005 to September 2020. Included in this study are all patients who underwent invasive UDS at RCWMCH during the study period. Patients were excluded from the analysis if studies were partially completed or in cases where data was missing from their records.

2.3 Data collection

From the request form completed by the referring clinician the following demographic and clinical information was retrieved: 1) patient demographic data at the time of UDS (age, sex,); 2) referring speciality; 3) the type of study (first study or follow-up); 4) primary diagnosis; 5) reason for referral; and 6) patient's current treatment (CIC, pharmacological, surgical). Missing data was accessed through the patient's hospital record. The UDS report for each patient was then reviewed and the following data was recorded. 1) Maximum cystometric capacity (expressed as % of expected bladder capacity); 2) presence of high risk features (low bladder compliance, DLPP $\geq$30 cm H_2O, NDO, DSD); and 3) VUR. The UDS findings were classified into normal, neurogenic, functional and anatomical. Study data was collected and

managed using REDCap electronic data capture tools hosted at University of Cape Town (redcap@uct.ac.za).

2.4 Definitions

‘‘Terminology adheres to standards recommended by the ICCS except where specifically noted[13].’’

End-fill detrusor pressure (EFP*)*: The baseline detrusor pressure recorded at the end of the filling phase, prior to commencement of voiding.

Low bladder compliance is defined as EFP greater than 20 cm H_2O (baseline detrusor pressure at the end of cystometry filling in the absence of detrusor overactivity) as a cut-off point. There are no standardised normal values for calculated compliance in children. This is because normal bladder capacity increases with age. This is lower than the most frequently quoted risk level of 40 cm H_2O. Of recent, many clinicians are revising this cut-off value and considering lower cut-off values to facilitate the chance of reversibility with treatment.

Expected bladder capacity (EBC*)*: EBC was calculated from the Hjalmas equation [*EBC= age (years) x 30 + 30 (expressed in ml)*] [12].

Definition of vesicoureteral reflux (VUR) is according to the International System of Radiologic Grading of VUR [15]:

I. **High grade VUR:** Refers to grade IV and V VUR
II. **Low grade VUR:** Refers to grade I, II and III VUR

2.5 Data analysis

The analysis was performed using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, Version 27.0. Before data analysis was carried out, the data was thoroughly cleaned and consistency checks made on each variable several times in order to ensure that all the data or major points under each had been captured. Continuous variables were expressed as range and median and the categorical variable as proportions n (%). p values

were calculated by, χ. test, or Fisher's exact test, as appropriate. p-value of 0.05 was considered statistically significant

2.6 Ethical approval

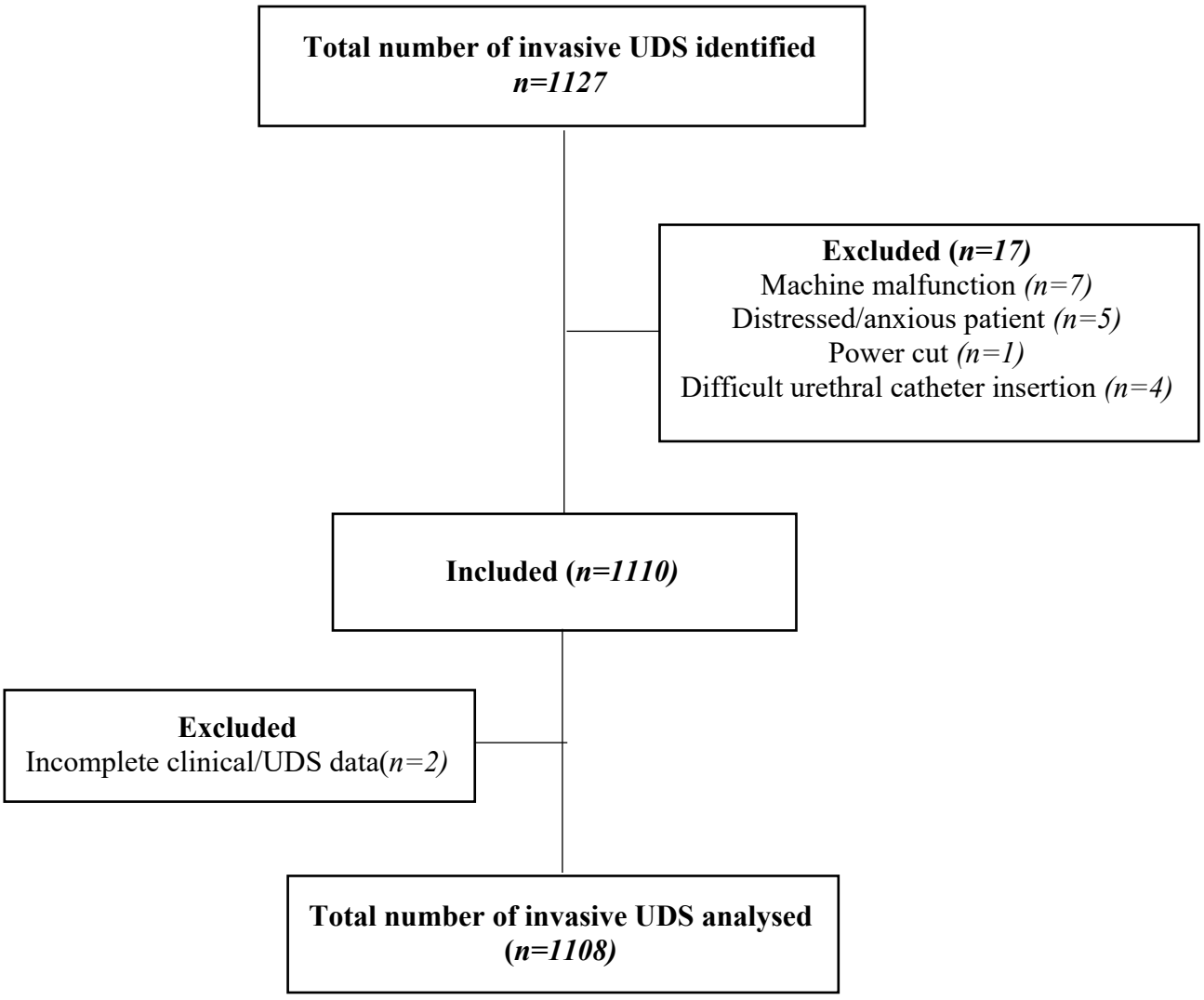
Ethical approval for this study was obtained from Human Research Ethics Committee, University of Cape Town *(HREC REF: 461/2020)* and Research Review Committee, Red Cross War Memorial Children's Hospital *(RXH: RCC 239)*.

3.0 Results

3.1 Study population and demographic characteristics

During the period under review, 1127 invasive urodynamic studies performed at RCWMCH were identified. As shown in **Fig. 1**, exclusions were predominantly incomplete studies due to machine malfunctioning (7/1127), power cuts (1/1127), difficult urethral catheterisation (4/1127) and an uncooperative child (5/1127). Only 2/1127 cases were excluded for lack of complete clinical and/or UDS data. This number may not be a true reflection of the total number of incomplete studies as unsuccessful studies conducted during the initial setup phase of the urodynamic unit were not recorded. Primary analyses were performed using 1108 UDS studies: 646 (58.3%) male patients and 462 (41.7%) female patients. They had a median age of 7.0 years (IQR) at time of study (see Table 1).

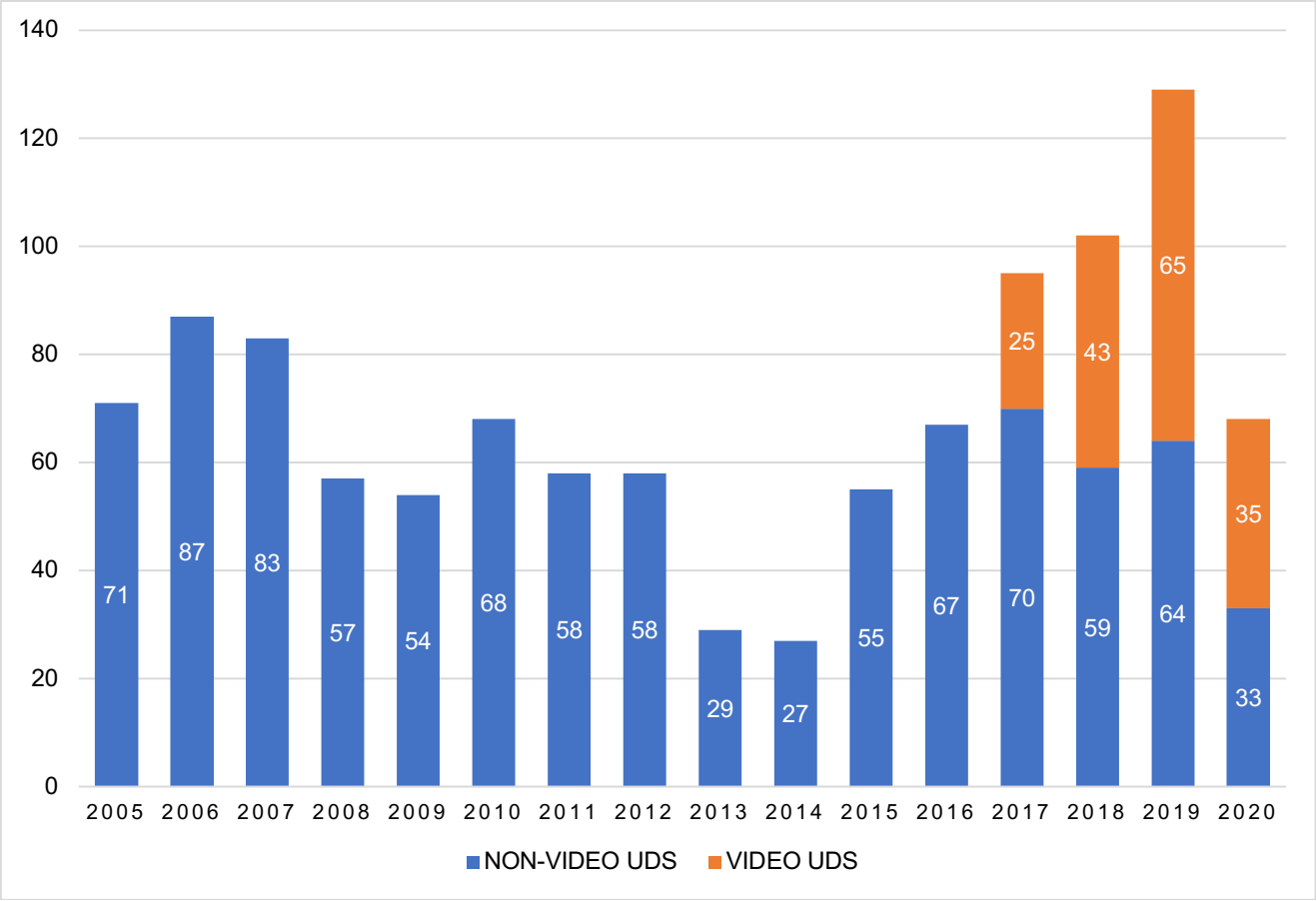
Fig. 1 Study flow diagram outlining the sequence of records selection for the study



3.2 Trend in the number of invasive urodynamics studies performed

Between 2005 and 2014, 592 studies were performed (mean, 59 per year). There is variation in the number of studies performed annually (see **Fig. 2**). This variation in UDS quantity has been influenced by several factors including delays and interruptions caused by servicing of machine in 2009, unit renovations between 2013 and 2014, and more recently Covid-19 pandemic in 2020. Although there is variation in quantity of UDS performed per year, on average the number of studies increased from 2015 through 2019 (mean, 90 per year).

Fig. 2 The number of invasive urodynamic studies performed at Red Cross War Memorial Children's Hospital by year



3.3 General characteristics of children

Table 1 also summaries the clinical characteristics and indication for UDS. The most frequent conditions seen included spinal dysraphism (myelomeningocele, myelocele, lipomyelocele, disatematomyelia) 646 (58.3%), PUV 153(13.8), sacral agenesis 57(5.1%), anorectal malformation 54 (4.9%), acquired spinal abnormalities (trauma, infections etc.) 52 (4.7%)

Table 1 Demographic and clinical information in children referred for urodynamic studies

Variable	*n*	%
Sex		
Male	646	58.3
Female	462	41.7
Age (years)		
Median (IQR)	7.0(4.0-11.0)	
Type of study		
First study	727	65.6
Follow-up study	381	34.4
Referral		
Spinal Defect Clinic	381	34.4
Urology	418	37.7
Nephrology	231	20.8
Other departments	78	7.0
Primary Diagnosis[1]		
Spinal dysraphism	646	58.3
Acquired spinal abnormalities	52	4.7
Anorectal Malformation	54	4.9
Sacral agenesis	57	5.1
PUV	153	13.8
Primary VUR	17	1.5
Enuresis	49	4.4
Other	144	13.0
Indication for UDS[2]		
Baseline	116	10.5
Recurrent UTI	206	18.6
VUR	124	11.2
Recurrent UTI + VUR	109	9.9
Review medical therapy	404	36.5
Review surgical treatment	94	8.5
Pre-surgical intervention	63	5.7
Pre- transplant	43	3.9
Post-transplant	34	3.1
Other	51	4.6

[1]Some children had multiple conditions, [2]Some children had multiple indications, IQR-interquartile range

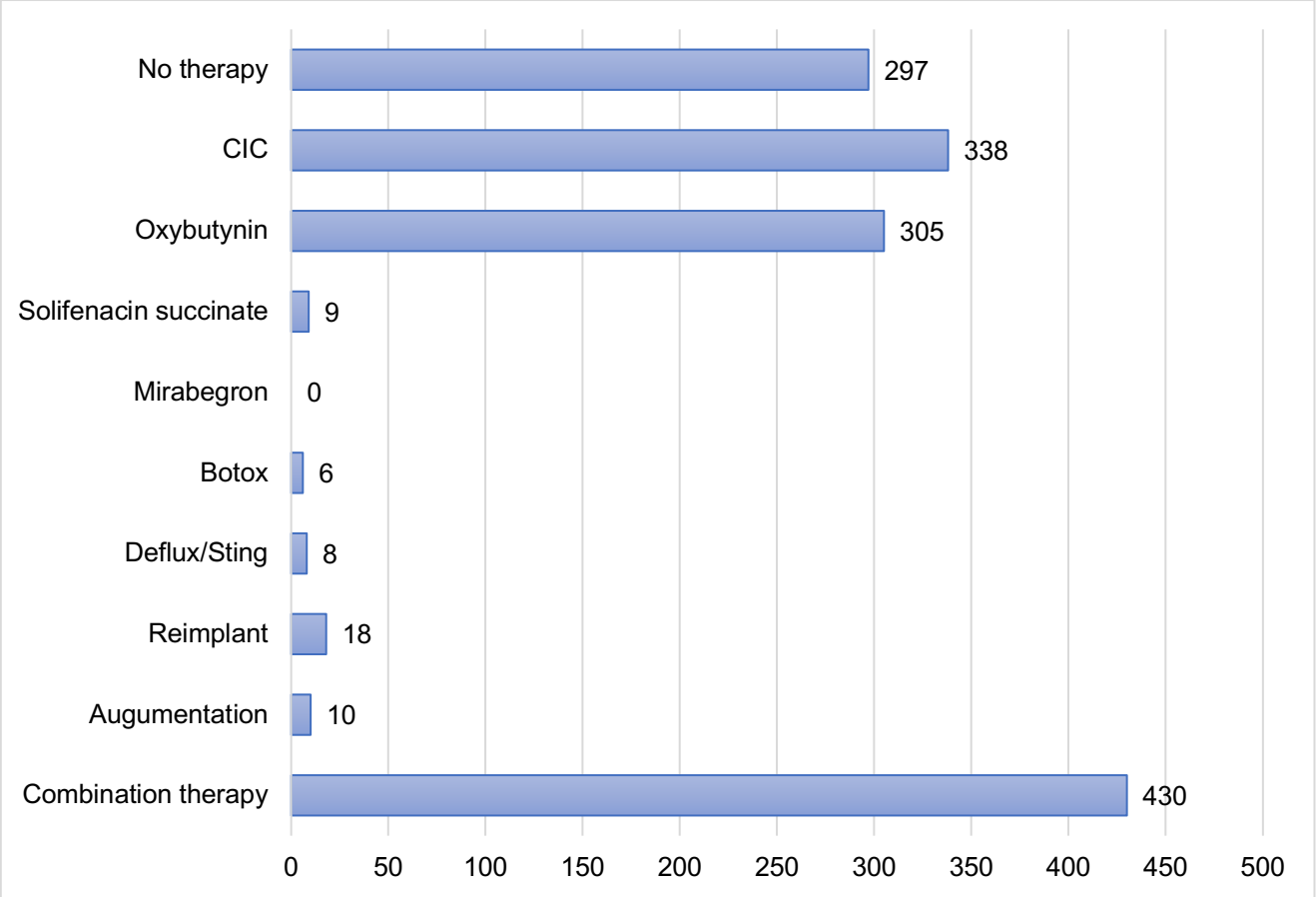
enuresis 49 (4.4%), primary VUR (1.5%), and other conditions (13.0%). More than one condition per patient could be present, for instance, a patient with spinal dysraphism could also have anorectal malformation. Referrals were received from various departments, the majority

coming from the Urology department (37.7%). The other sources of referral were Spinal defect clinic (34.4%), Nephrology (20.8%) and other departments (neurology, neurosurgery, oncology, other hospitals) (7.0%). The most common reason stated in the referral was review of medical treatment (36.5%).

3.4 Types of bladder intervention at first study

As shown in **Fig. 3**, a significant number of patients were already receiving some form of bladder intervention before their first UDS. The majority of the patients were receiving more than one type of bladder treatment 430 (59.1%). Of the 3 types of treatment (CIC, medical and surgical), CIC 338 (46.5%) was found to be the most common form of bladder management. 297 (40.9%) of the patients were not on any therapy at the time of their first UDS.

Fig. 3 The various types of bladder management at first study (*n=727*)

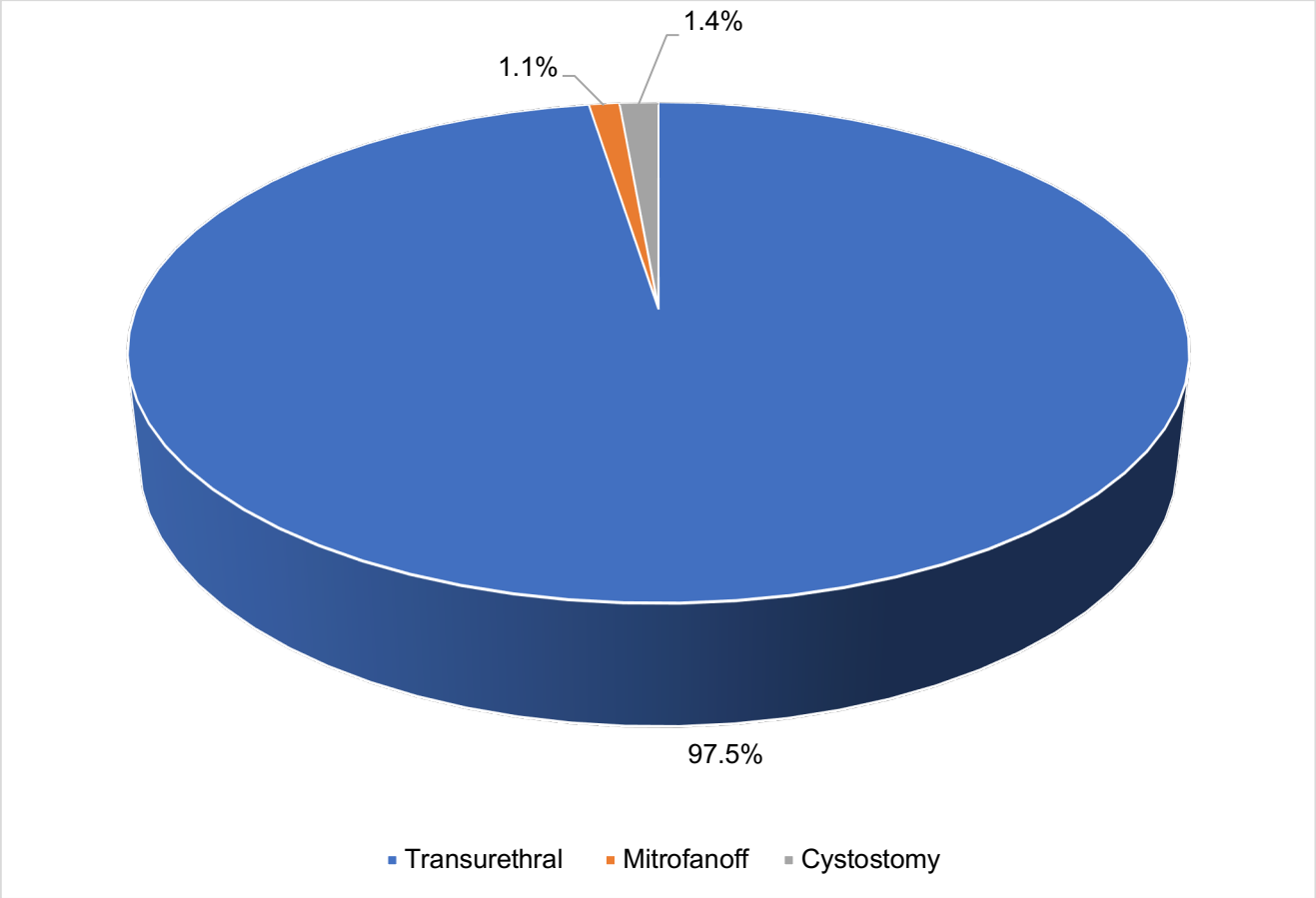


Combination therapy (more than one bladder treatment- CIC, surgical, medical)

3.5 Method of bladder catheterisation

Almost all (97.5%) of the patients had bladder catheters inserted urethrally (see **Fig. 4**). Other methods of bladder catheterization were used if the patient was already using the technique for bladder emptying.

Fig. 4 The technique used for bladder catheterisation



3.6 Urodynamic outcomes

The urodynamic diagnosis was neurogenic in 820 (74.0%), anatomical 135 (12.2%), functional 98 (8.8%) and normal 55 (5.0%). Table 2 shows the distribution of urodynamic data of the 4 groups. There was no significant age difference in all the 4 groups. Although the majority of the studies were performed in males, there was a female (69.4%) predominance in those with functional LUTD. Almost all those with anatomical LUTD were males (97.0%). UDS revealed low bladder compliance in 44.4% of all studies. Detrusor overactivity was recorded in 14.4% of UDS. VUR was detected in 54 out of 168 (32%) VUDS.

Table 2. Urodynamic outcomes

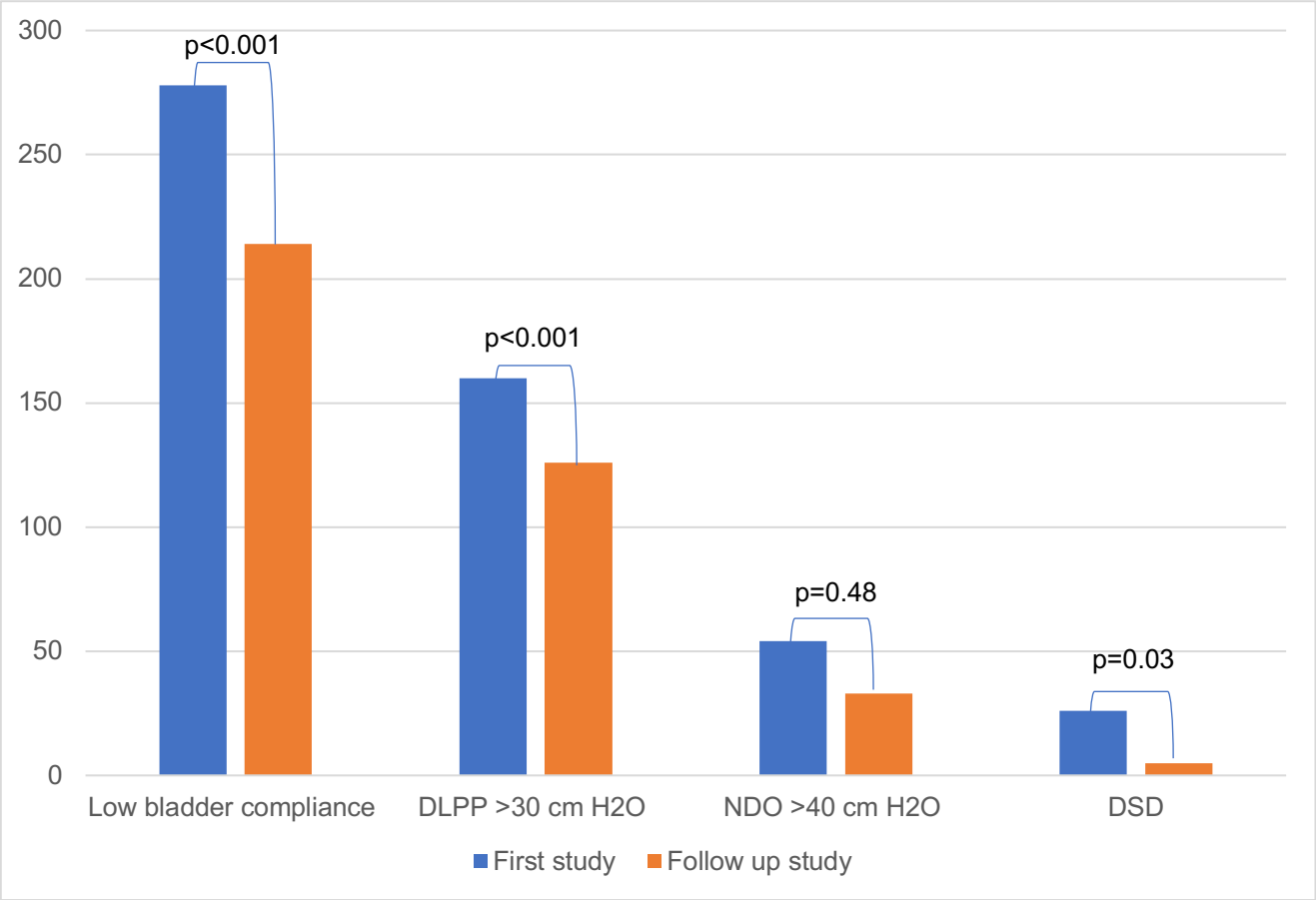
Variable	*Total (%) n=1108*	*Normal (%) n=55*	*Neurogenic (%) n=820*	*Functional (%) n=98*	*Anatomical (%) n=135*
Age (years)					
Median (IQR)	7.0(4.0-11.0)	6.0(1.0-10.0)	7.0(4.0-11.0)	8.0(6.0-11.0)	8.0(5-11.0)
Sex					
Male	646(58.3)	36(65.5)	449(54.8)	30(30.6)	131(97.0)
Female	462(41.7)	19(34.5)	371(45.2)	68(69.4)	4(3.0)
Incontinence pattern after age 5 years[1]					
Day time	422(53.9)	16(29.0)	329(40.1)	40(40.8)	38(28.1)
Night-time	460(58.8)	18(32.7)	353(43.0)	45(45.9)	43(31.9)
Both	490(62.6)	20(36.3)	374(45.6)	49(50.0)	49(36.3)
Maximum cystometric capacity (% of EBC)					
Small (< 65%)	325(29.7)	3(5.5)	275(33.5)	30(30.6)	17(12.6)
Normal (65-150%)	680(62.3)	52(94.5)	486(59.2)	47(48.0)	95(70.4)
Large (>150%)	87(8.0)	-	53(6.5)	13(13.2)	21(15.6)
Low bladder compliance	492(44.4)	-	420(51.2)	20(20.4)	52(38.5)
Detrusor activity					
Overactive	163(14.8)	-	87(10.6)	50(51.0)	26(19.3)
Underactive	50(4.5)	-	26(3.2)	20(20.4)	4(3.0)
VUR					
High	41(3.7)	-	21(2.6)	5(5.1)	15(11.1)
Low	13(1.2)	-	8(1.0)	4(4.1)	1(0.7)

[1] *n*= 782, *EBC*= [age (years) x 30 + 30 (expressed in ml)] for those >2years old and [7 x weight (kg) expressed in ml)] for those <2years old

3.7 High risk features for upper tract damage

With the exception of neurogenic detrusor overactivity (p=0.48), there was statistically significant improvement in low bladder compliance (p<0.001), detrusor leak point pressure >30 cm H_2O (p<0.001) and detrusor sphincter dyssynergia (p=0.03) between the first study and the study following therapeutic intervention (see **Fig. 5**).

Fig. 5 Comparison of bladder dynamics (high-risk features for upper tract damage) between the first and follow-up study



4.0 Discussion

The use of urodynamic studies in children has become increasingly popular in recent years, however there is limited literature concerning its use in sub-Saharan Africa. This study is a description of a 15-year experience with 1108 invasive urodynamic studies performed at Red Cross War Memorial Children's Hospital between September 2005 and September 2020. The most important findings of this study are the following: (1) the increasing trends in the use of UDS from 2015; (2) the wide range of indications for urodynamic testing; (3) presence of high risk urodynamic features at first study despite having previously been evaluated using the conventional modalities and receiving multiple bladder treatments; (4) a statistically significant improvement between first time study and follow-up study (post interventional) using low bladder compliance, detrusor sphincter dyssynergia (DSD) and detrusor leak point pressure (DLLP) >30 cm H_2O; and (5) the study also revealed the difficulties in treatment and management of children with LUTDs which may necessitate that multiple follow-up studies be carried to monitor response.

In the present study, the majority (58.3%) of UDS were performed on male patients with a median age at first study of 7.0 years (range 4.0-11.0 years). A similar sex difference was also reported by Hoebeke et al and Swithinbank et al. [11, 14]. The observed male predominance can be explained by the fact that LUTDs such as PUV, which accounted for 13.8% of all studies, only occur in male patients. Studies with a female predominance were mainly focusing on the use of UDS in children with NNLUTD such has urge syndrome, dysfunctional voiding etc [8, 9, 16].

The 15-year results showed increasing trends in the use of UDS. The observed upward trend from 2015 can be explained by the increase of knowledge surrounding the advantages of using the urodynamic studies when evaluating children with LUTD. Previous research corroborates the benefits of utilizing UDS for the diagnosis and management of children with neurogenic lower urinary tract dysfunction, including its superiority over traditional diagnostic modalities [5, 17-20]. When evaluating 51 patients with closed spina bifida, Johnston et al. demonstrated that clinical neurological assessment, history of voiding habit and renal tract ultrasonography were not reliable indicators of bladder dysfunction compared to VUDS [5]. Tarcan et al. reported that newborns with myelodysplasia and normal bladder function on urodynamics still

require follow-up urodynamic testing [17]. They also reported a 32% risk for urodynamic deterioration [17]. Several guidelines including the ICCS, European Association of Urology and the European Society for Paediatric Urology (EAU/ESPU) recommend urodynamic testing for all children with suspected neurogenic lower urinary tract dysfunction [4, 6].

Because of this compelling data on UDS in children with NLUTD, it is not surprising that the majority (62.1%) of urodynamic testing in this study were of children with spinal abnormalities. These included spinal dysraphism (myelomeningocele, myelocele, lipomyelocele, disatematomyelia) (52.3%), acquired spinal abnormalities (trauma, infections, metabolic and neoplasm) (4.7%) and sacral agenesis (5.1%). There may be a preferential referral from the multidisciplinary Spinal Defect Clinic at RCWMCH as the Urologists are the primary discipline at these clinics. A total of 37.7% studies performed were requested by the Urology department. There also seem to be a fair number of referrals coming from other departments, Spinal defect clinic 34.4%, Nephrology 20.8% and other (Oncology, Neurology, Neurosurgery, other hospitals) 7.0%. This finding suggests that the value of UDS has received heightened awareness even in specialties that have historically not involved it. Another notable finding is the small number 49 (4.4%) of patients referred with enuresis as an indication. This might be due to the fact that the centre currently has a tendency of undertaking uroflowmetry first for all functional LUTD and reserving invasive studies for patients not responding to treatment.

The justification for an invasive urodynamic study request is normally based on the assumption that the outcome is likely to affect treatment, when treatment does not lead to its intended outcome or when surgical interventions are planned [7, 10, 12, 21]. The benefits of performing a UDS should also outweigh the risks. The indications for the UDS studies performed are listed in Table 1. The most common reason for UDS were to discern treatment effects (medical 36.5% and surgical 8.5%). The study revealed that at first urodynamic study, 59.1% of children were already receiving more than one type of bladder management. It is evident from this finding that LUTD can be difficult to treat and often requires more than one type of bladder treatment. This observation also raises a concern of delayed referral for some patients. The ICCS advocates a baseline UDS before the age of one year for all patients with spinal dysraphism, even before symptoms start [4]. Early intervention is necessary to decrease significant complications such as end stage kidney disease in these cases. To improve early referral, there should be continued medical education on UDS and quality improvement

projects. CIC appears to be the most commonly used method of treatment. This reflects the hospital's institutional practice of CIC initiation in spinal dysraphism patients at an early age. The most frequently prescribed drug for bladder management was Oxybutynin (305 of 727), compared to Solifenacin succinate (9 of 727) and Mirabegron not being used in any patients in our study. Drug availability and cost might have influenced the choice of medication prescribed. Both Mirabegron and Solifenacin succinate were not available for use in our hospital during the study period as they are not on the drug formulary mainly due to their high cost. However, patients under medical aid cover were able to purchase the medications from private pharmacies.

The remaining UDS were ordered for recurrent UTI (18.6%), VUR (11.2%), baseline study (10.5%), recurrent UTIs associated with VUR (9.9%), pre- and post-transplant (7.0%), pre-surgical intervention (5.7%) and anorectal malformation (4.9%). The clinical significance of invasive UDS in children with NNLUTD still remain the source of controversy in literature [7, 9, 10]. Soygür et al. retrospectively evaluated the role of VUD in the diagnosis and management of voiding dysfunction and found that VUDS did not generally change approach to the patient [7]. In a multicentre controlled trial in children with urge syndrome and dysfunctional, Bael et al. recommends reserving VUD for those who have failed initial treatment [9]. Glazier et al. demonstrated abnormal VUDS in 28 out of 38 children with recurrent UTIs associated with voiding dysfunction [10]. In their study only 5 out of 38 had abnormal VCUG and KUB. From their study they strongly recommend VUDS to be considered in children with recurrent UTIs and a history of voiding dysfunction [10]. To address the current controversies in the additional value of UDS in children with NNLUTD, ICCS advocates for urodynamic testing in children with NNLUTD only if it will guide treatment plans and procedures [12].

There is controversy surrounding the method of bladder catheterization when performing a urodynamic examination. The concern regarding transurethral catheters is that it can affect urethral function and increase leak point pressure (LPP). However, several studies have demonstrated that the use of catheterization does not alter urethral function [22-24]. One such study is by Spinoit et al. which showed that transurethral catheters performed in a child-friendly outpatient clinic provides useful urodynamic information [23]. Most recently, Janssen et al. when comparing suprapubic and transurethral catheters to test urethral pressures in rats found no difference [24]. The ICCS Standardization Report on Urodynamic Studies of the Lower

Urinary Tract in Children recommends the use of either methods; however, risks should be weighed against benefit when the suprapubic route is used. In this study almost all (97.5%) urodynamic studies were performed with either a 6F or 7F double lumen transurethral catheters. Voiding phase is often assessed by performing a uroflow first and removal of the catheter after an invasive study, however this study did not determine the number of UDS where the voiding phase was assessed this way. The main reason for those performed using either Mitrofanoff (1.1%) or suprapubic catheter (1.4%) was because the patients were already using the technique for bladder emptying. The use of suprapubic catheterization is not a feasible option in a resource limited setting as it requires hospital admission with theatre time and monitoring space.

Although UDS usage has increased, concerns have been raised that the use of invasive urodynamic testing is not always justified in some patients. Only 5.0% of studies were reported as normal and this finding may reflect the appropriate use of UDS in children. This is comparable to Hoebeke et al and Johnston et al who reported 6% and 8% of normal studies respectively [5, 11]. Glazier et al. reported much higher incidence of normal studies when evaluating the utility of VUD in 42 children with UTI and voiding dysfunction [10]. Even though a significant number (430 of 727) of children were receiving more than on type of bladder treatment at first study, the study revealed low bladder compliance (278 of 727), DLPP >30 cm H_2O (160 of 727), neurogenic detrusor overactivity (54 of 727) and DSD (26 of 727). This reflects the difficulties in treating some of these patients and that UDS is often warranted to facilitate more specific diagnoses and guide treatment. The higher incidence of low bladder compliance (420 of 820), in those with NLUTD represents the importance of UDS in all patient with suspected NLUTD to identify those at risk for problems. ICCS advocates early urodynamic profiling in these patients and follow-up studies to allow early intervention and decrease significant complications. In this study the incidence of VUR could only be determined after introduction of VUDS, from year 2017. VUR was detected in 54 out of 168 (32%) VUDS. This study did not differentiate whether VUR was primary or secondary.

The clinical significance of performing a urodynamic testing has been demonstrated in this study. The overall goal of treatment of children with LUTDs is to preserve upper tracts and ameliorate or delay progression to ESKD especially in a setting where dialysis and transplantation may not be easily available. From the literature, factors associated with upper tract damage are low bladder compliance, DSD, neurogenic detrusor overactivity (NDO) and

DLPP >40 cm H_2O. With the exception of NDO (p=0.48), there was significant statistical improvement between the first study and follow-up study using low bladder compliance (p<0.001), DLPP >30 cm H_2O (p<0.001) and DSD (p=0.03). Based on this finding, the use of urodynamic examination in children with LUTDs has the potential to lower the incidence rate of renal replacement therapy.

The strength of this study is that it represents the largest number of invasive urodynamic studies in Sub-Saharan region. Another strength of this study is that it has defined variables using the ICCS definitions allowing comparison with other similar studies. It included a wide array of clinical indications and broader range of diagnosis. This study also included a diverse set of referring specialities. Nevertheless, this study is not without limitations. This was a single centre study but with large numbers. Other limitations relate to its retrospective design. Some UDS were excluded because of missing data and some studies may have been missed. Also, the incidence of DSD and VUR reported in this study may have been underestimated as they were periods where the centre was unable to perform electromyography and the use of VUDS started after year 2017.

In conclusion, this study has demonstrated an increased interest in the use of UDS in children. It has shown that UDS can guide in selecting most appropriate treatments for children with LUTD. It has highlighted the difficulties in the management of children with LUTDs which may necessitate that multiple follow-up studies be carried to monitor response. The recommendation of early and frequent follow-up UDS for children with spinal dysraphism recommended by ICCS may not be feasible in a resource limited country. For Africa this may mean early start on CIC, prioritizing patients based on their risk for upper tract damage and effective application of bladder and stool diaries, KUB (pre- and post-void residual volume) ultrasonography and VCUG.

5.0 Appendices

5.1 Appendix A. Data collection tool

Identification code: _____ **Study No.** _____

A. Gender? ☐ Male ☐ Female ☐ Unknown

B. Date of Birth? _____/_____/_____ (day/month/year) **Age:**_____

C. Date of the study? _____/_____/_____ (day/month/year)

D. ☐ **First study** ☐ **Follow-up study**

E. Primary Diagnosis

1. ☐ Open spinal dysrapism (MMC)
2. ☐ Closed spinal dysrapism
3. ☐ Sacral agenesis.
4. ☐ Anorectal malformation
5. ☐ Spinal tumors.
6. ☐ Spinal cord injury
7. ☐ Demyelinating disoders
8. ☐ PUV
9. ☐ Primary VUR
10. ☐ CKD + bladder dysfunction
11. ☐ CKD + dysplasia
12. ☐ CKD due to other causes
13. ☐ Neuropathic bladder
14. ☐ Dysfunctional voiding
15. ☐ Enuresis
16. ☐ Overactive bladder
17. ☐ Underractive bladder
18. ☐ ESRD of causes
19. ☐ Others

Comment: _____

F. Indication for the study

1. ☐ Baseline
2. ☐ Recurrent UTI
3. ☐ Daytime incontinence
4. ☐ Nighttime incontinence
5. ☐ VUR
6. ☐ HN/HUN
7. ☐ ? Neurogenic bladder
8. ☐ ? BOO
9. ☐ Pretransplant
10. ☐ Post-transplant
11. ☐ Pre-surgical intervention
12. ☐ Review medical therapy
13. ☐ Review surgical interven.
14. ☐ Others

Comment _____

G. CIC? ☐ Yes ☐ No

H. Bladder washouts ☐ Yes ☐ No

I. Oral medication ☐ Yes ☐ No

If yes ☐ Oxybutynin ☐ Vesicare ☐ Mirabegron

J. Surgical intervention: ☐ Yes ☐ No

If yes ☐ Botox ☐ Deflux/Sting ☐ AUG ☐ Reimplant

K. Urodynamic technique used:

1. ☐ CMG
2. ☐ CMG + PF
3. ☐ CMG + EMG
4. ☐ CMG + PF + EMG
5. ☐ Video CMG
6. ☐ Video CMG + PF
7. ☐ Video CMG + EMG
8. ☐ Video CMG + PF +EMG

L. Catheter placement: ☐ Transurethral ☐ other_____

M. Urodynamic study classification:

1. ☐ Normal
2. ☐ Neurogenic
3. ☐ NDO
4. ☐ Dysfunctional voiding
5. ☐ Overactive bladder
6. ☐ Underactive bladder
7. ☐ Bladder neck dysfuction
8. ☐ Stress urinary incontinence
9. ☐ Giggle incontinence
10. ☐ Vaginal reflux
11. ☐ Anatomical
12. ☐ Combined:

Comment _____

N. Presence of neurogenic high-risk features?

☐ Yes ☐ No ☐ Not applicable

If yes,

1. ☐ Low compliance (pdet >20cmH2O)
2. ☐ DLPP ≥30 cmH2O
3. ☐ NDO with >40cmH20
4. ☐ DSD
5. ☐ Combined

Comment _____

O. Anatomical (if VUD) ☐ Yes ☐ No ☐ Not applicable

If yes

1. ☐ High grade VUR
2. ☐ Low grade VUR
3. ☐ PUV
4. ☐ Diverticulae
5. ☐ Fixed outlet obstruction
6. ☐ Ureterocele

P. Comments _____

_____

5.2 Appendix B. Ethical approval documents

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18 August 2020

HREC REF: 461/2020

Dr A Coetzee
Division of Paediatric Nephrology
Paediatric and Child Health
Red Cross War Memorial Children's Hospital
Rondebosch
Email: ashton.coetzee@uct.ac.za
Student: dintletn@yahoo.com

Dear Dr Coetzee

PROJECT TITLE: A 15-YEAR RETROSPECTIVE REVIEW OF URODYNAMIC STUDIES IN CHILDREN AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH), CAPE TOWN, SOUTH AFRICA (MPHIL CANDIDATE: DR TD MOSALAKATANE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 and 06 July 2020.

Approval is granted for one year until the 30 August 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Thembisile Mosalakatane will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

HREC 461/2020sa

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 461/2020sa

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES

Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30-11-2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	12/11/21

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	06-11-2021		
HREC REF Number	HREC:461/2020	Current Ethics Approval was granted until	30-08-2021
Protocol title	A 15-YEAR RETROSPECTIVE REVIEW OF URODYNAMIC STUDIES IN CHILDREN AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH), CAPE TOWN, SOUTH AFRICA		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	☐ No ✓
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	DR ASHTON COETZEE		

Department / Office Internal Mail Address	ashton.coetzee@uct.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☒ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please (tick ☐)appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ☐***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☒
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	N/A
Billing Address of Sponsor:	N/A
Vat Number:	N/A

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Contact person	N/A
Telephone number	
Email Address	
2. **Internal Journal Billing:**	
Fund Number:	N/A
Cost Centre Number:	N/A
Account Holder Name:	N/A
Division of Account Holder:	

2. List of documentation for approval

3. Protocol status (tick □)

□	Open Enrolment
□	Closed to enrolment (tick □)
□	Research-related activities are ongoing
□	Research-related activities are complete, long-term follow-up only
N/A	Research-related activities are complete, data analysis only
□	Main study is complete but sub-study research-related activities are ongoing
□	Study is closed □ Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	N/A
Number of participants enrolled, since last HREC Progress report (continuing review)	N/A
Additional number of participants still required	N/A

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	N/A

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

6. Cumulative summary of participants

Total number of participants who provided consent	N/A
Number of participants determined to be ineligible (i.e. after screening)	N/A
Number of participants currently active on the study	N/A
Number of participants completed study (without events leading to withdrawal)	N/A
Number of participants withdrawn at participants' request (i.e. changed their mind)	N/A
Number of participants withdrawn by PI due to toxicity or adverse events	N/A
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	N/A
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	N/A
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	N/A

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Currently doing final write-up,

8. Protocol violations and exceptions (tick ☐ all that apply)

☒	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ☐ all that apply)

☒	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
NIL

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☒ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ☐)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	☒ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☒ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☒ No
If yes, please explain:	

12. Level of risk (tick ☐)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☒	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
N/A

13. Insurance

Please confirm that valid no fault insurance is still in place? (tick ☐)			
☐ Yes		☒ No	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via **fhs.sponsorship@uct.ac.za** ***regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.***			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ☐)	
☐ Yes	☒ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	10/11/2021

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

5.3 Appendix C. RCWMCH Approval Letter

Western Cape Government
Health

DR AN PARBHOO
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

28 August 2020

Dr T Masalakatane
Senior Registrar
Paediatric Nephrology

Dear Dr Masalakatane,

RESEARCH: RXH: RCC 239

PROJECT TITLE: A 15-YEAR RETROSPECTIVE REVIEW OF URODYNAMIC STUDIES IN CHILDREN AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH), CAPE TOWN, SOUTH AFRICA

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Kindly note that this approval is subject to strict adherence to the HREC recommendations regarding research involving participants during COVID-19, dated 17 March 2020 (UCT HREC notice attached).

Yours sincerely,

DR AN PARBHOO
MANAGER: MEDICAL SERVICES

www.westerncape.gov.za

6.0 References

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