FULL/ LONG TITLE OF THE STUDY

A longitudinal cohort study of urological complications predictable by pre-transplant lower urinary tract symptoms

SHORT STUDY TITLE/ ACRONYM

Study of Complications Predictable by pre-transplant LUTS (SCOPE)

PROTOCOL VERSION NUMBER AND DATE

Version 1.4 9th December 2025

RESEARCH REFERENCE NUMBERS

IRAS Number:	xxxxx
Sponsor:	NHS Greater Glasgow and Clyde
Sponsor Protocol Number:	xxxxxx

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature Date:

Name (print):

Chief Investigator:

Signature: Date:

Name (print):

LIST of CONTENTS

KEY STUDY CONTACTS

Chief Investigator	David Kingmore Department of Renal Surgery Queen Elizabeth University Hospital Glasgow Telephone: +44 (0) 141 451 6211 Email: david.kingsmore@ggc.scot.nhs.uk
Sponsor's Representative	Dr Adam Wade Admin Building, Level 2 Administration building Gartnavel Royal Hospital 1055 Great Western Road Glasgow Telephone: +44 (0) 141 314 4343 Email: adam.wade@nhs.scot
Sponsor	NHS Greater Glasgow and Clyde
Funder(s)	XXXXXXXX
Key Protocol Contributors	Mr Dhruv Satya Sahni, Urology Research Fellow, Glasgow Prof Imran Ahmad, Consultant Urologist, Glasgow Dr Martin Shaw, Statistician, Glasgow Ms Emma Aitken, Consultant Transplant Surgeons, Glasgow

SCIENTIFIC SUMMARY

Research questions:

1. What is prevalence and distribution of lower urinary tract symptoms (LUTS) in the renal transplant population?
2. Is there an association between pre-transplant LUTS scores and urological adverse outcomes following transplantation?

Background:

Urological consultation is an essential step in the pre-operative workup for patients before placing them on a waiting list for a renal transplant. The aim of this workup is to diagnose, treat and optimize any pre-existing urological pathology to maximize post-transplant graft function. Pre-existing lower urinary tract symptoms (LUTS) are common in patients with end stage renal disease (ESRD). Similarly, post-transplant urinary tract infection (UTI) is the most encountered complication. The European Association of Urology (EAU) recommends comprehensive lower urinary tract evaluation of patients prior to renal transplant. However the evidence on which these recommendations are based is limited and there is no standardized pathway followed across centers globally.

Aims and Objectives:

1. **Primary objectives:**
    a. To understand the distribution of LUTS score in patients undergoing renal transplantation
    b. To describe the distribution of LUTS scores across adverse outcomes post-transplant

2. **Secondary objectives:**
    - To determine if there is a difference in distribution of LUTS scores between male and female patients
    - To assess whether the presence of moderate to severe LUTS predict the occurrence of post-transplant significant urological complications in the 6 weeks and 12 months following transplantation.
    - To evaluate whether the presence of moderate-severe LUTS can predict graft outcomes in the 12 months following transplantation
    - To determine if duration of time on the transplant waiting-list and/ or RRT vintage and/or anuria predict objective change in LUTS or adverse urological outcomes post-transplant

- To determine if pre-existing urological conditions increase the likelihood of major urological complication following transplant
- To compare transient and persisting change in graft renal function over 12 months between patients with and without pre-transplant.
- To determine whether changing the peri-operative work-up pathway to evaluate pre-operative LUTS, will reduce the likelihood of urological complications in the year following transplant
- To inform sample size calculation and end points of a future larger intervention randomized trail

Methods:

A prospective single center longitudinal feasibility study to evaluate LUTS in patients at the time of waitlisting, day of transplant, 6 weeks and 1 year post transplant and evaluate the impact on post-operative urological complications will be undertaken.

The study will be conducted in two parts:

1. Evaluation of patients beginning on day of transplant, prospectively at 6 weeks and 1 year
2. Evaluation of patients at time of waitlisting, prospectively 1-year post-waitlisting (if not yet transplanted), on day of transplant and at 6 weeks and 1-year post-transplant

We aim to approach all patients at the time of transplant and at the time of transplant wait-listing to be consented.

All patients who consent will undergo baseline assessment of LUTS (clinical history, validated questionnaires, Uroflowmetry and Post Void Residual measurement). For patients who do not produce enough urine to provide a sample for Uroflowmetry (130mls), urinary catheter or flexible cystoscope will be used to fill the bladder and perform the study.

Where clinically indicated, patients will undergo invasive urodynamic studies.

The use of invasive urodynamics (filling cystometry) will be reserved for following patients:

1. Diagnostic uncertainty despite the clinical history, questionnaires and non-invasive urodynamics.
2. Failure to provide a diagnostic uroflowmetry on 2 occasions despite using cystoscopy to fill the bladder.

3. If initial workup reveals a possibility of neurogenic lower urinary tract dysfunction (NLUT)

Repeat assessment of symptomatology, urological complications and graft function will be assessed at 6 week and 1 year post-transplant.

LUTS will primarily assessed using IPSS for male participants and ICIQ-FLUTS for female participants (see below), supplemented by post-void residual volume and urine flow studies.

The "urological complication" will be a composite any of the following occurring within the first 12 months following transplantation:

1. Urinary retention defined as high post-void residual volumes initiating need for indwelling catheter (IDC)/ clean intermittent catheterization (CISC) within the first 12 months of transplantation. (This will include patients who fail trial of void post-surgery).
2. Recurrent culture-proven urinary tract infections (≥3 in the first 12 months post-transplant)
3. Ureteric leak or suspected ureteric leak requiring surgical or radiological intervention
4. Deterioration in renal function (eGFR, Creatinine) due to post-renal causes:
   - Transient decline in renal function (>20% from nadir creatinine)
   - Persistent decline in renal function (>10% from nadir creatinine)
5. Sepsis of urinary source requiring hospital admission (including graft pyelonephritis)
6. Any patient undergoing any surgical or radiological intervention for a urological complication (excluding routine stent removal post-transplant) within the first 12 months of transplantation
7. Graft loss as a result to urological complications within the first year of transplantation

Secondary outcomes will include:

1. Evidence of urological complications in the 6 weeks following transplantation.
2. Evaluation of whether the presence of moderate-severe LUTS can predict graft outcomes in the 12 months following transplantation
3. Determination if the duration of time on the transplant waiting-list and/ or RRT vintage and/or anuria predict objective change in LUTS or adverse urological outcomes post-transplant

4. Whether or not pre-existing urological conditions increase the likelihood of major urological complication following transplant
5. Compare patients undergoing this work-up regimen with an age/ sex matched historical cohort to determine if there is any difference in risk of post-operative urological complications with a focused pre-operative screening regimen.
6. Determination of whether changing the peri-operative work-up pathway to evaluate pre-operative LUTS, will reduce the likelihood of urological complications in the year following transplant

Timeline for delivery:

Recruitment will commence in January 2026 and is anticipated to continue for 2 years. Follow-up will cease when all patients recruited are > 1 year post-transplant; have been removed from the transplant waiting-list or will have died.

Anticipated impact and dissemination:

It is anticipated that results will directly impact patient care and help stratify patients before transplantation. This will allow us to implement bladder optimizing protocols to maximize post-transplant graft function.

The results will be presented at international platforms and will be published in high-impact medical journals, which will help fill a lacuna in the literature. This may pave way for a future multicenter interventional study.

ABBREVIATIONS

PLAIN ENGLISH SUMMARY

Many patients with kidney failure need a kidney transplant. Some of these patients will have problems relating to the storage or passage of urine. In many cases this is unrecognized before transplant, especially if the patient no longer passes urine. This can lead to problems after the transplant, resulting in infections, complications and poor kidney function.

There are very few studies which have looked at how issues with the patient's urinary tract and bladder affect the outcome of kidney transplant. However, it's well-recognized amongst kidney transplant surgeons to be a significant problem. This study aims to determine the number of patients who have undiagnosed waterworks issues before transplant and investigate if these issues make it more likely for the patient to have urinary tract infections, poor kidney transplant function or other complications in the year following transplant.

We will approach everyone having a kidney transplant in Glasgow within a two-year period: both when they join the transplant waiting list and when they receive a transplant. We will follow patients up at 6 weeks and 1 year after transplant, taking measures of bladder function from history, questionnaires and simple studies of urine flow/ bladder function. We hope to recruit 100 patients over in each group over a two year period.

Currently there is no standardized suggested work-up of the bladder and urinary tract prior to kidney transplant. Different transplant centers do different things and there is no agreed best approach. We hope that results from this study might better inform how and why a patient's lower urinary tract should be assessed before transplant. In doing so, we hope to reduce complications and improve outcomes for after transplant. If we find that there are identifiable problems pre-transplant that predict complications after transplant, we'd hope that the results of this study could inform a larger study in the future where we could intervene on these issues pre-transplant to see if it prevents complications in the future. However, at the moment, we don't know what to measure or how best to intervene. It's hoped that this study would help us better understand these issues

FUNDING:

ROLE OF STUDY SPONSOR

The trial is sponsored by NHS Greater Glasgow and Clyde.

The sponsor is responsible for ensuring that proper arrangements are in place to initiate, manage, monitor and finance the study in line with the Research Governance Framework and Good Clinical Practice.

Specifically, the sponsor is responsible for ensuring that:

- the trial is appropriately assessed and resourced
- the trial is conducted to the required standards and conforms with regulatory requirements
- There is adequate provision for compensation and indemnity in the event of harm to research participants.

Some of these responsibilities will be delegated to the Chief Investigator.

The sponsor will maintain oversight for all aspects of the trial and will be responsible for monitoring trial progress.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study Steering Groups

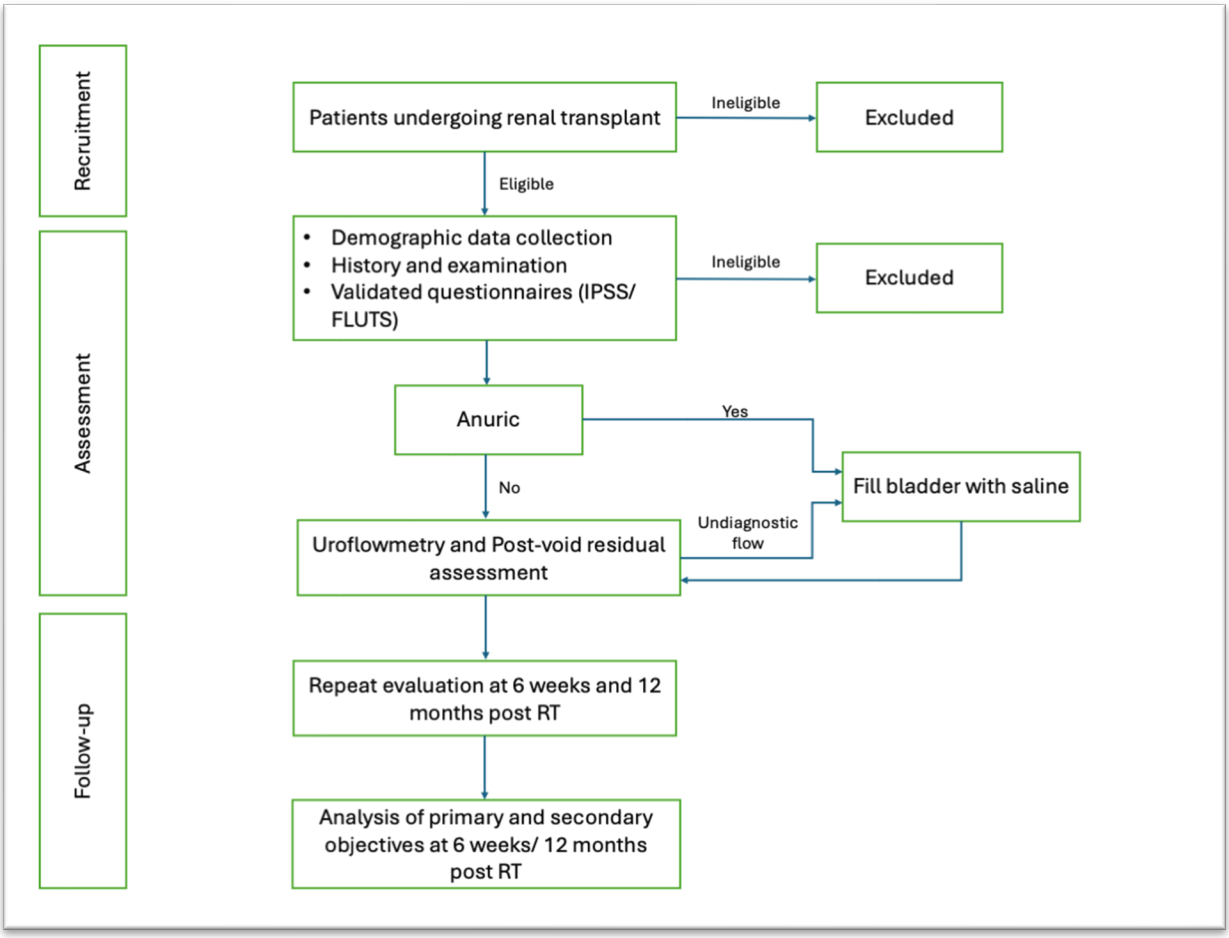
An oversight committee which includes representatives of the research team, an interested independent clinician and a patient representative will be assembled to oversee the project; ensure milestones are reached and to identify emerging findings. The study steering group will meet online every 12-24 weeks and minuted outcomes will be described

PROTOCOL CONTRIBUTORS

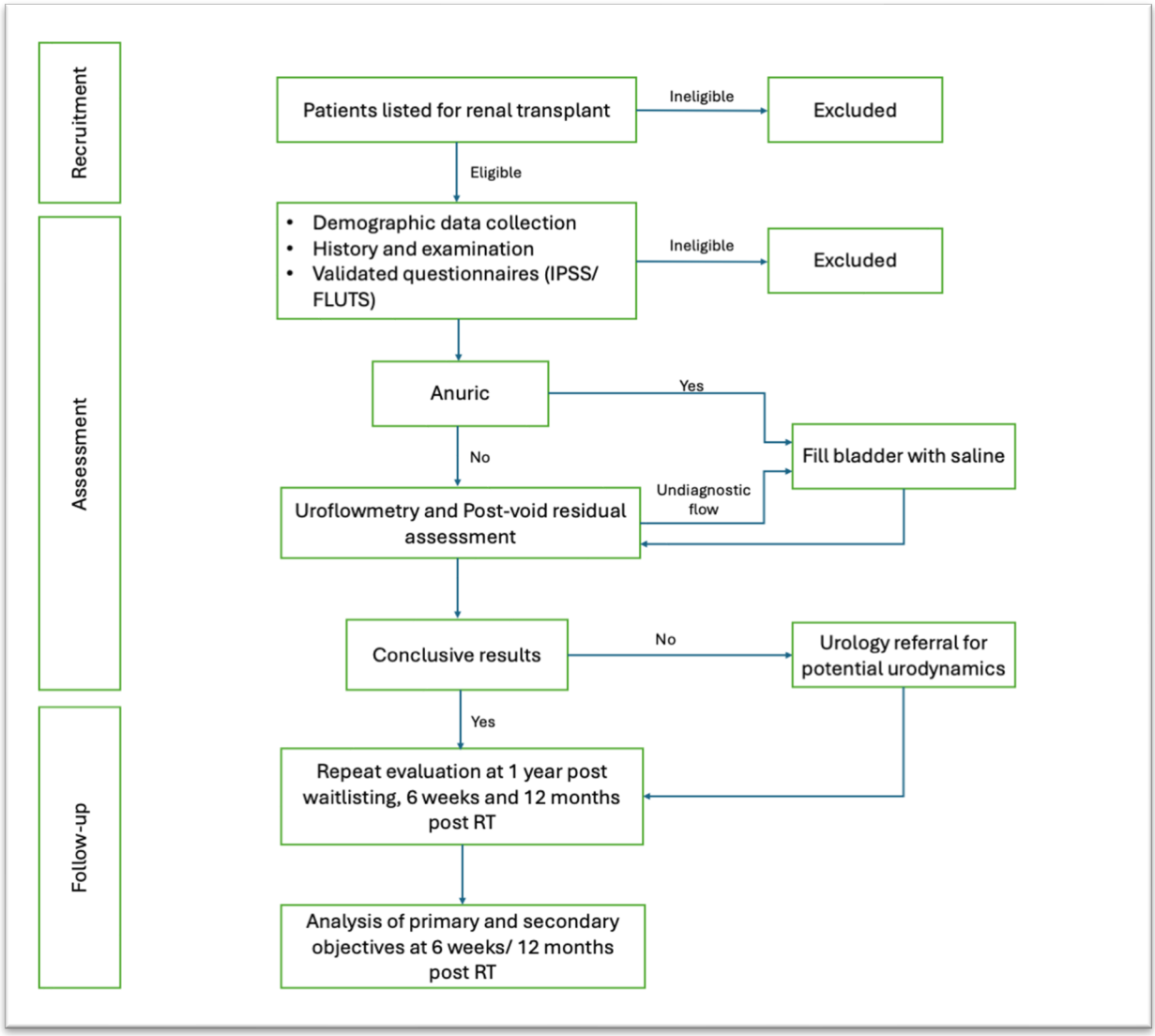
The protocol was written by the Mr Dhruv Satya Sahni with oversight from the Chief Investigator David Kingsmore and Emma Aitken and input from the coinvestigators (Prof Imran Ahmad and Dr Martin Shaw). The project sponsor is NHS Greater Glasgow and Clyde.

TRIAL FLOW CHART

Phase 1: Patients recruited at time of kidney transplant



Phase 2: Patients recruited at time of waitlisting



1. BACKGROUND

Over the last few decades, the incidence of End Stage Renal Disease (ESRD) has increased exponentially[1]. Kidney disease significantly impacts the longevity and quality of life with survival worse than most malignant conditions. Although renal replacement therapies (RRT) like dialysis and transplantation can improve survival rates, the improvement in quality of life remains complex and difficult to assess[2]. Renal transplantation (RT) provides the best therapy available to this cohort of patients, offering superior survival and quality of life compared to long term dialysis[3].

In the lead up to the procedure, the evaluation and management of both renal transplantation donors and recipients is a multidisciplinary effort. From the early days of transplant surgery, urologists have been closely involved in all stages. The world's first successful renal transplant involved John Hartwell Harrison, a urologist who performed the donor nephrectomy in 1954[4].

Although only 1.4-5% of ESRD is directly attributable to a urological cause, it's likely that many more patients have urological factors at play in their pathology, with multiple aspects of renal transplantation closely linked with urological knowledge and experience[5]. Urological complications such as Urinary Tract Infections (UTIs), urinary retention, ureteric anastomotic strictures, and vesicoureteral reflex (VUR) are common and can significantly impact graft function[6]. Additionally, patients have been anuric for a period prior to transplantation.

The advancements in surgical techniques, immunosuppression regimens and enhanced recovery protocols have led to a remarkable increase in success rates for both cadaveric and living donor transplantation[7,8]. This has gradually shifted the focus towards reducing peri-operative and long-term complications what may potentially compromise graft function and patient quality of life (QoL). In this vein, a frequently underestimated but highly clinically relevant issue is bladder dysfunction or dysfunctional bladders (DB). DB can occur secondary to reduced renal function (i.e. many of these patients have been anuric for a period prior to transplantation; the impact of this bladder "disuse" is poorly understood); secondary to other causes of renal failure e.g. diabetes, hypertension; or from physical alterations in the urinary tract, which include bladder outlet obstruction, neurogenic bladder and urinary lithiasis[9,10].

Furthermore, life expectancy advances have led an increase to the number of older people with ESRD undergoing RT. The UK Renal Registry consistently shows a trend towards increasing median ages for patients undergoing renal transplant. The median age of renal transplantation in men in UK was 46 years and 55 years in Scotland[1,11]. In men

> 50 years of age, Lower urinary tract symptoms (LUTS) secondary to Bladder outlet obstruction (BOO) primarily caused by Benign Prostate Hypertrophy (BPH) linearly increases with age[12]. LUTS generally present as symptoms related to urinary storage (increased urinary frequency, urgency, nocturia, incontinence) or urinary voiding (poor stream, hesitancy, incomplete emptying etc.). Symptoms of these relative common conditions can be masked in patients with renal failure due to oligo-anurisis. Urodynamic studies indicate that prolonged disuse of bladder may lead to structural and functional changes including reduced bladder compliance and impaired detrusor contractility[9]. LUTS can arise after RT leading to restoration of diuresis; potentially posing a serious risk to graft function[13].

Several researchers have advocated for investigation and treatment of bladder function before RT owing to the high prevalence of these symptoms in pre-transplant patients. However, there is a paucity of prospective data linking LUTS with post RT urological complications and significant variability in practice within the UK and Europe regarding pre-operative evaluation of patients and no clear guidance on a standardized protocol[5,13,14].

2. RATIONALE

The current literature is based only on a few retrospective studies, which explore the incidence and risk factors for post RT urological complications. However, none of them have investigated whether pre-existing bladder symptoms serve as a predictive marker of complications. Although some of these studies may provide an insight, they have not examined this using a longitudinal approach using standardized validated tools. There is a critical lack of research employing a prospective, longitudinal approach which employs validated tools such as International Prostate Symptoms score (IPSS) and, in particular no work in women looking at the International Consultation on Incontinence Questionnaire (ICIQ-FLUTS) for female LUTS[15–17].

This study aims to address this gap by prospectively evaluating the prevalence and distribution of LUTS within the RT population and understand how these scores are distributed across a range of urological complications. .

By stratifying patients individually by their urological risk and employing relevant screening and treatment strategies, we seek to develop a standardized pathway for pre-transplant screening which can then be utilized in a future interventional study to determine if outcomes are modifiable.

3. OBJECTIVE AND OUTCOME MEASURES/ ENDPOINTS

Primary objectives

The primary objectives are twofold:

a. To understand the distribution of LUTS score in patients undergoing renal transplantation
b. To describe the distribution of LUTS scores across adverse outcomes post-transplant

Secondary objectives

- Evidence of urological complications in the 6 weeks following transplantation.
- Evaluation of whether the presence of LUTS can predict graft outcomes in the 12 months following transplantation
- Whether or not pre-existing urological conditions increase the likelihood of major urological complication following transplant
- Compare patients undergoing this work-up regimen with an age/ sex matched historical cohort to determine if there is any difference in risk of post-operative urological complications with a focused pre-operative screening regimen.
- Determination of whether changing the peri-operative work-up pathway to evaluate pre-operative LUTS, will reduce the likelihood of urological complications in the year following transplant
- To assess the change in LUTS and QOL by validated tools at 6 weeks and 1 year post RT after re-establishment of diuresis.
- To assess whether duration of time on the waiting list/ presence of anuria impacts on primary outcomes and change in severity of LUTS/ QoL. Inform future end points, sample size, trial design etc. of a future interventional study
- Determination if the duration of time on the transplant waiting-list and/ or RRT vintage and/or anuria predict objective change in LUTS or adverse urological outcomes post-transplant

Primary outcome measures

LUTS will primarily assessed using IPSS for male participants and ICIQ-FLUTS for female participants (see below), supplemented by post-void residual volume and urine flow studies.

"Urological complication" will be considered to be a composite any of the following occurring within the first 12 months following transplantation:

1. Urinary retention defined as high post-void residual volumes initiating need for indwelling catheter/ clean intermittent catheterization within the first 12 months of transplantation. (This will include patients who fail trial of void post-surgery).
2. Recurrent culture-proven urinary tract infections (≥2 in the first 6 months/ ≥3 in the first 12 months post-transplant)
3. Ureteric leak or suspected ureteric leak.
4. Deterioration in renal function (eGFR, Creatinine) due to post-renal causes:
   - Transient decline in renal function (>20% from nadir creatinine)
   - Persistent decline in renal function (>10% from nadir creatinine)
5. Sepsis of urinary source requiring hospital admission (including graft pyelonephritis)
6. Any patient undergoing any surgical or radiological intervention for a urological complication (excluding routine stent removal post-transplant) within the first 12 months of transplantation
7. Graft loss as a result to urological complications within the first year of transplantation

Secondary outcome measures

- Renal function at 12 months (eGFR, creatinine) and its association with presence and severity of pre-transplant LUTS
- Change in IPSS/ ICIQ-FLUTS scoring from baseline to 6 weeks and 1 year post RT (including QoL scores)

Table of endpoints/ outcomes

Objectives	Outcome Measures	Timepoints
Primary Objective:		
To determine the prevalence of distribution of pre-transplant LUTS	LUTS at baseline as assessed by IPSS/ ICIQ-FLUTS, flow studies and post-void residual urine volumes	Baseline
To determine the distribution of LUTS scores across adverse urological complications post-transplant	Incidence of urological complications (retention, recurrent UTIs, ureteric obstruction, need for CIC, graft pyelonephritis etc as above)	6 weeks and 12 months post-transplant
Secondary Objectives:		
To assess change in LUTS over time (includes QoL)	IPSS/ ICIQ total score and QoL sub-score, post-void residual volumes, Qmax	Baseline, 6 weeks, 12 months
To describe urological complications in patients with and without LUTS	Frequency and type of complications	6 weeks and 12 months
To correlate pre-transplant LUTS with graft function	Renal function measures (eGFR, creatinine)	6 weeks, 12 months
Impact of waiting times on outcomes	IPSS/ ICIQ total score and QoL sub-score	12 months post wait listing

4. STUDY DESIGN

This is an observational longitudinal cohort study. Two separate patient cohorts will be considered:

1. Those approached for consent at time of transplant: baseline, 6 weeks post-transplant and 1-year post transplant measurements will be obtained
2. Those approached for consent at time of wait-listing: baseline values at time of wait-listing, time of transplant, 6 weeks and 1 year post transplant will be obtained.

5. STUDY SETTING

The study will be conducted within the West of Scotland Renal Transplant Unit and NHS Greater Glasgow and Clyde Urology. This is a high-volume tertiary center with a dedicated renal transplant program catering to entire Scotland. This center works in close association with Urology and Nephrology departments making it an ideal site for conducting a multidisciplinary longitudinal study.

6. PARTICIPANT ELIGIBILITY CRITERIA

Inclusion criteria

All adult patients (≥18 years old) scheduled to undergo first time renal transplantation (both deceased and living donor candidates).

Exclusion criteria

- Unable or unwilling to provide consent
- Patients undergoing re-transplant (to avoid confounding because of previous interventions)
- Patients undergoing simultaneous urological reconstructive procedures
- Patients with previously reconstructed bladders (includes Augmentation cystoplasty, ileal conduit, neobladder etc.)
- Significant cognitive impairment which would limit their capacity to accurately report symptoms

In line with NIHR guidance on equality, diversity and inclusion all people regardless of gender, sexual orientation, pregnancy, ethnicity, religion and socioeconomic status will be offered the same opportunity to participate. Hospital translators will be used where appropriate to obtain consent and the HR-QoL tools employed are available in a large variety of languages. Where it may not be possible to provide a translated HR-QoL tool, this will not serve as a contraindication to participation should the patient wish to, rather this secondary outcome measure will be omitted from data collection.

Both for equity and for scientific integrity, it's important that roughly equal numbers of men and women complete the study (as men will complete an IPSS and woman a ICIQ-FLUTS). Recruitment will be reviewed after 70 patients and patients targeted based on gender to ensure a fairly equal number of male and female participants.

7. TRIAL PROCEDURES

This is a prospective, single center, longitudinal cohort study. Two separate patient cohorts will be considered:

3. Those approached for consent at time of transplant: baseline, 6 weeks post-transplant and 1-year post transplant measurements will be obtained
4. Those approached for consent at time of wait-listing: baseline values at time of wait-listing, time of transplant, 6 weeks and 1 year post transplant will be obtained.

Patients will be recruited over a two-year period and followed-up until they are one year post-transplant; removed from the transplant waiting list or have died.

We aim to approach all patients at the time of transplant and at the time of transplant wait-listing to offer participation.

This is primarily an observational study. History, examination and all perioperative follow-up will be conducted as would be standard of care. No additional hospital visits are required as the transplant assessment visit, transplantation, 6 week and 12 month follow-up visits will all coincide with regular clinical care.

Recruitment

Participant identification

Participants will be identified by a member of the clinical team either at time of referral for transplantation or at the time an offer of a kidney transplant offer is made. A member of the research team with be contacted and the patient screened for eligibility.

Screening

Case note review of patients' past medical and vascular access history will be undertaken by the research team to determine if eligibility criteria are met. If eligibility criteria are met, a PIS will be provided and the patient offered the opportunity to discuss the study further with the research team.

If a patient is screened but is not eligible for the trial, an anonymous record of the case will be kept in the screening log. The screening log will collect patient initials, age, and gender, date of screen failure and reason for screen failure. The screening log will be kept in the ISF.

Consent

The Principal Investigator (PI) will retain overall responsibility for the conduct of research at their site, which includes the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is undertaken then details should be recorded within the delegation log of the ISF.

A member of the research team will obtain informed consent prior to the undertaking any trial intervention. The exact timing for obtaining informed consent may vary between patients and will depend on the expediency of transplantation.

Wherever possible, patients will be provided with at least 24 hours to read the PIS, consider the information and ask questions. For patients recruited at time of transplant listing, this will be simple, and PIS will be sent out along with other routine information regarding transplantation prior to the clinic appointment, as is our standard practice. For patients recruited at the time of transplant admission, it can be more challenging to provide >24 hours of time for patients to consider participation within a research study, due to the expedient nature of transplantation. This is an issue that we commonly encounter consenting for trials for transplantation. Information regarding the trial will be placed on the unit's patient facing website and app so that interested patients will have access to the trial information prior to admission for transplantation. Beyond this, patients will be given as long as reasonably possible to consider their options and discuss them with research and clinical teams, acknowledging that a decision regarding participation must be made prior to transplantation (which in the case of deceased donor transplantation can happen in the middle of the night with <24 hours' notice). Patients will be encouraged to read the PIS fully consider the information provided, ask

questions and reflect as appropriate. However, the patient also has the right to make an immediate decision to consent.

All patients have the right to refuse participation without giving reasons. Participants remain free to withdraw from the trial at any time without giving reasons and without prejudicing his/her further treatment. If a patient declines to consent a record of this will be made within the patient notes and in the SCOPE study screening log.

Once signed, a copy of the consent form will be given to the patient; the original kept in the local ISF and a copy placed in the patient notes. The informed consent discussion will be recorded in the participant's medical notes including the version number of the PIS provided to the participant.

Patients recruited into the trial will be assigned a unique patient identifier allowing participant to be identified i.e. 001 on all future trial documentation. An enrolment log will be maintained in the ISF to permit identification of patient names against trial numbers for those recruited to the trial. The ISF will be retained at a secure location within the Renal Transplant Unit. The enrolment log is the only place where patient identifiable information will be recorded. Upkeep and security of the ISF is the responsibility of the PI.

Interventions/ trial procedures

The interventions within this study beyond standard care are the bladder diary, IPSS/ ICIQ-FLUTS questionnaire, a bladder scan (bedside ultrasound) to measure post-void residual volume and non-invasive uroflowmetry studies. These additional interventions will be performed at time of transplant listing (where appropriate), after 1 year on the transplant waiting list (where appropriate), on the day of transplant, 6 weeks and 12 months after transplantation.

A small number of patients will not pass sufficient urine to perform flow studies/ and or urodynamics. These patients will require their bladder to be pre-filled with sterile saline prior to voiding in order to achieve an accurate reading. A protocol for how to undertake this is outlined in Appendix 1 and would be performed by the ward doctor as part of clinical care. The rates of bladder filling and urodynamic studies being performed within trial will be monitored by the Trial Steering Committee at 3- 6 monthly intervals to ensure that these are clinically appropriate.

Study visits

A schedule of study visits is outlined below. All study visits will correspond to pre-existing clinical visits.

For patients recruited on day of transplant:

Study assessments	**Visits**			
	Screening visit	**Enrollment visit (Day of transplant or day -1)**	**Week 6 +/- 2 weeks**	**Week 52 +/- 4 weeks**
Assessment against eligibility criteria	**X**			
Provision of PIS	**X**			
Informed consent		**X**		
Demographics and past medical/ urological history		**X**		
Bladder diary		**X**	**X**	**X**
IPSS/ICIQ		**X**	**X**	**X**
Bladder diary		**X**	**X**	**X**
Renal function		**X**	**X**	**X**
Uroflowmetry[+]		**X**	**X**	**X**
Post-void residual[+]		**X**	**X**	**X**
Urodynamics[++]		**(X)**	**(X)**	**(X)**
Urological complications			**X**	**X**
Other secondary outcome measures			**X**	**X**

For patients recruited in the transplant assessment clinic:

Study assessments	Visits					
	Screening visit	Enrollment visit (Transplant assessment)	1-year post-waiting listing*	Day of transplant or day -1)	Week 6 +/- 2 weeks	Week 52 +/- 4 weeks
Assessment against eligibility criteria	X					
Provision of PIS	X					
Informed consent		X		X		
Demographics and past medical/ urological history		X	X	X		
Bladder diary		X	X	X	X	X
IPSS/ICIQ		X	X	X	X	X
Bladder diary		X	X	X	X	X
Renal function		X	X	X	X	X
Uroflowmetry+		X	X	X	X	X
Post-void residual+		X	X	X	X	X
Urological complications					X	X
Other secondary outcome measures					X	X

Data collection

Data will be collected from standardized data collection tools as outlined in section 7 and from within the Scottish Renal Electronic Record (SERPR).

Demographics, past medical and surgical history

*Patient factors: A*ge, Gender, Ethnicity, BMI, Postcode

Relevant past medical history: Diabetes, Hypertension, Ischemic heart disease, cause of primary renal disease; RRT vintage; prior transplantation and duration of same; reason for prior graft loss if previous transplant

Past and present urological history: Any prior urological diagnosis/ interventions/ surgery; native urinary output; any prior urological assessment of bladder function/ volumes; LUTS symptoms (storage- frequency, urgency, nocturia, voiding- dribbling, struggling to initiate, incomplete emptying), caffeine and fluid intake, previous/ current use of catheters, previous urological surgeries, use of medications for LUTS (anticholinergics, 5-alfa reductase inhibitors, alfa agonists, intravesical Botulinum Toxin-A)

Transplant specific factors: Donor age, gender, any pre-existing/ known urological history in donor or anatomic irregularity with kidney e.g. duplex collecting system, dual transplant, horseshoe kidney, renal stones, renal cysts etc.), DBD/ DCD/ live donor, CIT, cRF, immunosuppressive regimen and induction agent, other relevant aspects of post-transplant course e.g. DGF, primary non-function, biopsy-proven rejection and treatment for same; documented operative complications with initial surgery

Bladder diary

We will be using the form prescribed by ICIQ (https://iciq.net/iciq-bladder-diary)

IPSS/ ICIQ-FLUTS

LUTS will be assessed by taking a complete urological history and using validated, gender appropriate questionnaires:

- Males: We will use the International Prostate Symptoms score (IPSS). Moderate to severe LUTS will be defined if the score is above 7[15].
- Females: We will the International Consultation on Incontinence Questionnaire – Female Lower Urinary Tract Symptoms (ICIQ-FLUTS). It does not have a total score, but instead measures the severity of following subscales separately:
  - Incontinence 0-20
  - Voiding 0-12
  - Filling 0-16

Whilst there is no official cutoff for severity for ICIQ-FLUTS, we aim to use the following cutoffs based on the published evidence[17–19]:

- Mild: total score 0–11
- Moderate: 12–23
- Severe: 24+

This stratification will ensure an accurate gender-specific assessment of baseline urinary symptoms and will allow the results to be meaningful, across subgroups having external validity.

Post-void residual bladder volume

This is a routine bedside test which uses a non-invasive ultrasound "bladder scanner" to measure how much urine is left in the bladder after a patient has urinated. The patient is asked to go to the bathroom to void urine and the urine void is captured and measured. Immediately following the urine void, a bladder scan of the residual (remaining) fluid levels within the bladder is made.

As some renal patients have been on dialysis for many years, there is a chance that a small number are anuric or do not make sufficient urine to make this scan reliable. In these situations (where the patient is able to pass less than 130ml at a single void), a cystoscopy (telescope test) will be performed to fill the bladder with fluid artificially and then the patient asked to void and the test repeated to ensure that an accurate result is obtained.

Uroflowmetry

This is a non-invasive test which measures the quality and strength of a patient's urine flow and can help detect problems with the bladder outflow. While the patient is passing urine, the urine is captured within a jug on a scale, and this lets us assess "real-time" what is going on with the urine flow. Measurements such as Qmax (the maximal flow rate), time to fully empty the bladder, and the shape of the flow trace can be helpful in assessing the patient's bladder outflow. This test would be conducted at that the same time and in the same manner as the urine voided for the post-void residual.

Occasionally, the urine flow is "non-diagnostic". This can happen in cases where patients are anxious or the bladder is inadequately filled. If this is the case, the patient would be encouraged to drink some fluid and the study repeated +/- filling cystoscopy.

Invasive urodynamics (filling cystometry)

We do not intend on performing invasive urodynamics on every patient, only where clinically indicated. That clinical indication is likely to be detected elsewhere within the transplant work-up process (i.e. out with the study) but would include:

1. Diagnostic uncertainty persists despite the clinical history, questionnaires and non-invasive urodynamics.
2. Failure to provide a diagnostic uroflowmetry on two occasions despite using cystoscopy to fill the bladder
3. If initial transplant workup reveals a possibility of neurogenic lower urinary tract dysfunction (NLUTD).

If available as part of the clinical course, relevant invasive urodynamic data (bladder capacity, compliance, sphincter assessment, detrusor contractility, pressure-flow study, urodynamic diagnosis etc.) will also be captured.

8 STATISTICS AND DATA ANALYSIS

Sample size

This is a non-interventional, exploratory study, the results of which we hope will may inform a future interventional study. The primary aims are two-fold:

a. To understand the distribution of LUTS score in patients undergoing renal transplantation
b. To describe the distribution of LUTS scores across adverse outcomes post-transplant

Our sample size has been chosen based on three factors:

1. Feasibility within the anticipated timescale
2. The likelihood of obtaining a representative distribution of LUTS scores assuming a relatively normal distribution from other feasibility studies
3. The existing literature (it'll be the largest observational study of evaluating LUTS in transplant patients, and the only one to evaluate longitudinally)

We aim to recruit 100 patients into each of the two parts of the study over two years.

The Glasgow Renal Transplant Unit performs 100-150 renal transplants annually and assesses over 200 patients per year. Conservatively, over a two year period, 100 patients could be recruited by approaching and consenting less than half of those transplanted and fewer than 25% of those assessed for transplantation.

We anticipate a 5-10% death rate (as would be standard in the transplant population). We do not anticipate that patients will be lost to follow-up as they all come back to regular post-transplant clinics, but assuming 5-10% withdraw or have incomplete data sets that should still leave a minimum of 40 men and 40 women with complete datasets for evaluation.

There is little data on the prevalence or distribution of LUTS in the renal transplant population in men[15-17], and no data in women. Based on the previous two year's data from our own center we anticipate that between 50-60% of patients will have one of the composite urological complication outcomes. (We have deliberately chosen a broad definition of "urological complications", with high prevalence, for this initial study so that

all possible relevant outcomes are considered so that all relevant outcomes are considered and recorded. This could be refined for future interventional studies to be more specific if deemed appropriate.)

We aim to describe both IPSS (male) and ICIQ-FLUTS (female) in combination and separately. We would therefore hope to achieve roughly similar numbers of males and females recruited into the study. We'd therefore aim to evaluate recruitment after 70 patients and if gender distribution were unequal, target as required.

We anticipate it should be large enough to allow for 5-10% death rate (as would be standard in the transplant population). We do not anticipate that patients will be lost to follow-up as they all come back to regular post-transplant clinics but assuming 5-10% withdraw or have incomplete data sets. This is primarily an exploratory study. Little data exists about the prevalence of LUTS in renal/kidney transplant recipients. It is anticipated that the results of this study will inform sample size calculations for future interventional studies.

Data collection

All data will be collected within a password protected Microsoft Excel spreadsheet stored on an NHS-password protected computer. No patient identifiable information will be included within that spreadsheet only unique patient identifiers.

Data analysis

Data analysis will be exploratory with the primary aims of describing the distribution of LUTS scores for males and females and determining the prevalence of urological complications. These factors could inform sample size calculation, determine the correct primary endpoint for a future interventional study.

If appropriate, we may/ may not attempt to:
- Investigate the relationship between LUTS severity and urological complications

- Describe any change in LUTS whilst on the transplant waiting list/ post-transplant

- Establish a risk model for urological complications post-transplant.

9 ETHICAL AND REGULATORY CONSIDERATIONS

Research Ethics Committee

The trial protocol and study documents have been reviewed and received a favourable opinion from XXX (REC).

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (amendments may also need to be reviewed and approved by the NHS R&D departments before they can be implemented in practice at local sites).
All correspondence with the REC will be retained by the CI.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the trial.

If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report to the REC with the results, including any publications/abstracts.

Other Regulatory Review

The trial shall not commence until a favourable ethical opinion has been obtained from the Research Ethics Committee and the Regulatory "Green Light" given by the Sponsor NHS Greater Glasgow and Clyde.

For any substantial amendment to the study the Chief Investigator, in agreement with the sponsor and the Study Steering Committee, will submit information to the REC for review and approval. The Chief Investigator or designee will work with the local R&D department so the necessary arrangements can be put in place to implement the amendment to confirm their support for the study as amended.

Within 90 days after the end of the study, the Chief Investigator will, on behalf of the Sponsor, ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The Chief Investigator will supply the Sponsor with a summary report of the clinical study, which will then be submitted to the REC within one year after the end of the study.

Peer review

The project was reviewed by two experts (Andrew Jackson, Consultant Transplant Surgeon, Queen Elizabeth Hospital, Glasgow and Rachel Thomas, Consultant Transplant Surgeon, Queen Elizabeth University Hospital, Glasgow). It was also reviewed by the West of Scotland Renal Patient Involvement and Engagement group.

Assessment and management of risk

This is essentially an observational study. It is not anticipated that patients will be subjected to any additional investigations over and above those of standard care. The rate of "filling cystoscopy", invasive urodynamics and any complications arising from the same will be monitored by the Trial Steering Committee at 3-6 monthly intervals throughout the trial. Any change in the rates of these procedures arising within the trial, will be discussed with the Chief Investigator.

Patient Involvement and Engagement

PPIE is integral to the design, implementation, governance and dissemination of this study ensuring that the question being asked is important, outcomes appropriate and design acceptable to potential participants. PPIE undertaken in line with INVOLVE (2013) values and principles.

The study protocol and Patient Information documentation was discussed at the West of Scotland Renal Patient and Public Engagement Group and received positive feedback. The comments received have been taken into account to design this protocol.

Data protection and participant confidentiality

All investigators will comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulations (GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All patients will be assigned a unique patient identified. All data will we stored within a single Excel file on a password protected NHS computer. Patient identifiable information (name, date of birth, CHI/ NHS number, address will be recorded in the enrolment log and retained in the ISF. This is the only place where patient identifiable information will be recorded. Secure storage of ISFs at individual sites will be the responsibility of the PI. Original consent forms will be retained within the ISF. These forms will be available to regulatory bodies and sponsor for inspection upon request.

Patient questionnaires will be scanned into patient case notes following coding within the Excel spreadsheet and will form part of the patient's clinical record. At the end of the study the original questionnaires will be destroyed. Anonymised data will be archived within a recognised data repository at the end of the study.

Indemnity

This is a clinician-initiated study sponsored by NHS Greater Glasgow and Clyde. The sponsor is a member of the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS) which covers the Sponsors legal liability in relation to clinical research, this includes clinical negligence and harm from study design.

Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Access to the final study dataset

The final study dataset will be deposited in the UK Data Archives and be made available to researchers with an interest in the outcomes.

10 DISSEMINIATION POLICY

Dissemination policy

Ownership of the results resides equally with the three primary investigators. On completion of the study, the data will be analysed and a Final Study Report prepared for REC +/- any funders. All collaborators will have the right to publish from the data. No time limits are on publication from the publication from the data.

All participants of the study will be given the opportunity to read the final report in advance and comment on it. The project team will endeavour to take their feedback into account in the final draft of the final report. Data from the final report will be available through UK Data Archives.

Results will be presented at national and international transplant conferences as well is within the Patient Forum of UK Kidney Week. Scientific publication will take place in peer reviewed journals. Additionally infographics will be created summarising key results and disseminated via patient groups and charities e.g. Kidney Research UK and Kidney Care UK

11 REFERENCES

1 https://webarchive.nrscotland.gov.uk/20241112193232/https://publichealthscotland.scot/publications/scottish-renal-registry/scottish-renal-registry-annual-report-2024/. Scottish Renal Registry (2024) Annual Report.

2 Hakeem Ismael N, Omer Rashid A. Health-Related Quality of Life in End-Stage Renal Disease Patients and Healthy Individuals. *Galen medical journal* 2020; 9: e1987.

3 Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; 341: 1725–30.

4 HARRISON JH, MERRILL JP, MURRAY JE. Renal homotransplantation in identical twins. *Surg Forum* 1956; 6: 432–6.

5 Power RE, Hickey DP, Little DM. Urological evaluation prior to renal transplantation. *Transplant Proc* 2004; 36: 2962–7.

6 Choate HR, Mihalko LA, Choate BT. Urologic complications in renal transplants. *Transl Androl Urol* 2019; 8: 141–7.

7 Tan JHS, Bhatia K, Sharma V, et al. Enhanced recovery after surgery recommendations for renal transplantation: guidelines. *Br J Surg* 2022; 110: 57–9.

8 Van Meerhaeghe T, Murakami N, Le Moine A, Brouard S, Sprangers B, Degauque N. Fine-tuning tumor- and allo-immunity: advances in the use of immune checkpoint inhibitors in kidney transplant recipients. *Clin Kidney J* 2024; 17: sfae061.

9 Nahas WC, Mazzucchi E, Antonopoulos I, et al. End-stage renal disease and bladder dysfunction: algorithm for renal transplantation. *Transplant Proc* 2001; 33: 2984–5.

10 Djakovic N, Wagener N, Adams J, et al. Intestinal reconstruction of the lower urinary tract as a prerequisite for renal transplantation. *BJU Int* 2009; 103: 1555–60.

11 https://www.ukkidney.org/audit-research/annual-report/26th-annual-report-data-31122022. 26th UK Renal Registry (2022) annual report.

12 Verhamme KMC, Dieleman JP, Bleumink GS, et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care--the Triumph project. *Eur Urol* 2002; 42: 323–8.

13 Mitsui T, Shimoda N, Morita K, Tanaka H, Moriya K, Nonomura K. Lower urinary tract symptoms and their impact on quality of life after successful renal transplantation. *Int J Urol* 2009; 16: 388–92.

14 van der Weide MJ, Hilbrands LB, Bemelmans BL, Meuleman EJ, Frederiks CM. Lower urinary tract symptoms after renal transplantation. *J Urol* 2001; 166: 1237–41.

15 Cockett ATK. The International Consultation on Benign Prostatic Hyperplasia. Paris, France: World Health Organization, 1992.

16 Brookes ST, Donovan JL, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. *Am J Obstet Gynecol* 2004; 191: 73–82.

17 Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* 2004; 23: 322–30.

18 Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen C-I, Wein AJ. Global prevalence and economic burden of urgency urinary incontinence: a systematic review. *Eur Urol* 2014; 65: 79–95.

19 Ku JH, Jeong IG, Lim DJ, Byun S-S, Paick J-S, Oh S-J. Voiding diary for the evaluation of urinary incontinence and lower urinary tract symptoms: prospective assessment of patient compliance and burden. *Neurourol Urodyn* 2004; 23: 331–5.

APPENDIX 1

Procedure for undertaking bladder filling in patients who are anuric/ significantly oliguric/ unable to provide enough sample

Indication: Any patient who is anuric, passes <250ml (a cupful of urine per day) or feels bladder is full to void with <130ml on pre-void bladder scan

Procedure: A small (ideally 12F) catheter (single use or long-term) is inserted into the bladder and the bladder filled *passively* with 250ml of sterile saline. It is important that the bladder is filled passively and the saline bag is not squeezed. Once the bladder has 250ml of saline contained within, urine flow studies will be performed as standard. The bladder will be emptied with the same catheter if the patient is unable to void themselves. In case patient reports severe discomfort whilst filling the bladder, the procedure should be stopped and can be reattempted later.

If catheter insertion is unsuccessful: A flexible cystoscope can be used as an alternative to gain access to the bladder. If it is not possible to insert either catheter or flexible cystoscope, the operating surgeon should be contacted (as formal urological input may be required to facilitate catheterization pre-transplantation), documentation made in the patient notes and the test consider equivocal.

Recording results: The pre- and post-void bladder scan results and trace from the flow dynamics study should be included within the *nursing notes* (so that the trace can be scanned into the clinical portal)

Abnormal/ equivocal findings:

For equivocal bedside tests carried out on the day of transplantation, the operating surgeon should be informed of any equivocal results, but transplantation should proceed as anticipated with view to early post-operative Urology referral for consideration of Urodynamics.

For equivocal bed side tests carried out in pre-assessment clinic, transplant listing should be delayed until satisfactory Urology opinion has been obtained after due investigations.