CLINICAL STUDY PROTOCOL

TrUST

Transplant Ureteric Stent Trial

Protocol Version: 2 **ISRCTN.** 09184595

REC number: 10/H0718/5 **R&D number:** RJ1 10/N067

Study Title: Transplant ureteric stent removal: Early versus standard removal. A Randomised controlled trial.

Investigational Product: N/A

Chief investigator (CI)	Jonathon Olsburgh Consultant Transplant & Urological Surgeon, Guy's and St Thomas' NHS Trust, London
CI's address	Renal Offices, 6th Floor Borough Wing, Guy's Hospital, St Thomas Street, London, UK. SE1 9RT
Telephone	0207188 8476
Email	Jonathon.Olsburgh@gstt.nhs.uk

Study Sponsor	Guy's & St Thomas' NHS Foundation Trust, Karen Ignatian
Address	Research & Development Office, Guy's Hospital, Great Maze Pond, London, UK. SE1 9RT
Telephone	0207188 5736
Fax	02071881295
Email	Karen.Ignatian@gstt.nhs.uk

Co-investigators: Mr Geoff Koffman, Consultant Transplant Surgeon, Guy's and St Thomas' NHS Foundation Trust, London

Mr Nizam Mamode, Consultant Transplant Surgeon, Guy's and St Thomas' NHS Foundation Trust, London

Dr Manish Sinha, Consultant Paediatric Nephrologist, Evelina Childrens Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Dr Stephen Marks, Consultant Paediatric Nephrologist, Great Ormond Street NHS Trust, London

Professor Janet Peacock, Professor of Medical Statistics, Department of Primary Care and Public Health Sciences, King's College London

Professor David Beighton, Professor, Dental Microbiology, Kings College London

Dr Carolyn Hemsley, Consultant Microbiologist, Guy's and St Thomas' NHS Foundation Trust, London

Prof Ali McGuire, Professor in Health Economics, London School of Economics, London

Dr Michelle Webb, Consultant Nephrologist, East Kent Hospitals University NHS Foundation Trust, London.

Dr Iain Macdougall, Consultant Nephrologist, King's College London NHS Foundation Trust, London.

Study Location: Multicentre (GSTT & Evelina, GOSH, KCH, K&C)

Medical contact: Jonathon Olsburgh

Medical Contact on site: Local investigators named above

Research Fellow: Miss Pareeta Patel, Clinical Research Fellow, Guy's & St Thomas' NHS Foundation Trust, London.

Trial Nurse: Ms Golda-Grace Azanu, Research Nurse, Guy's & St Thomas' NHS Foundation Trust

Trial Email: TrUST@gstt.nhs.uk

Funder: NIHR - Research for Patient Benefit grant

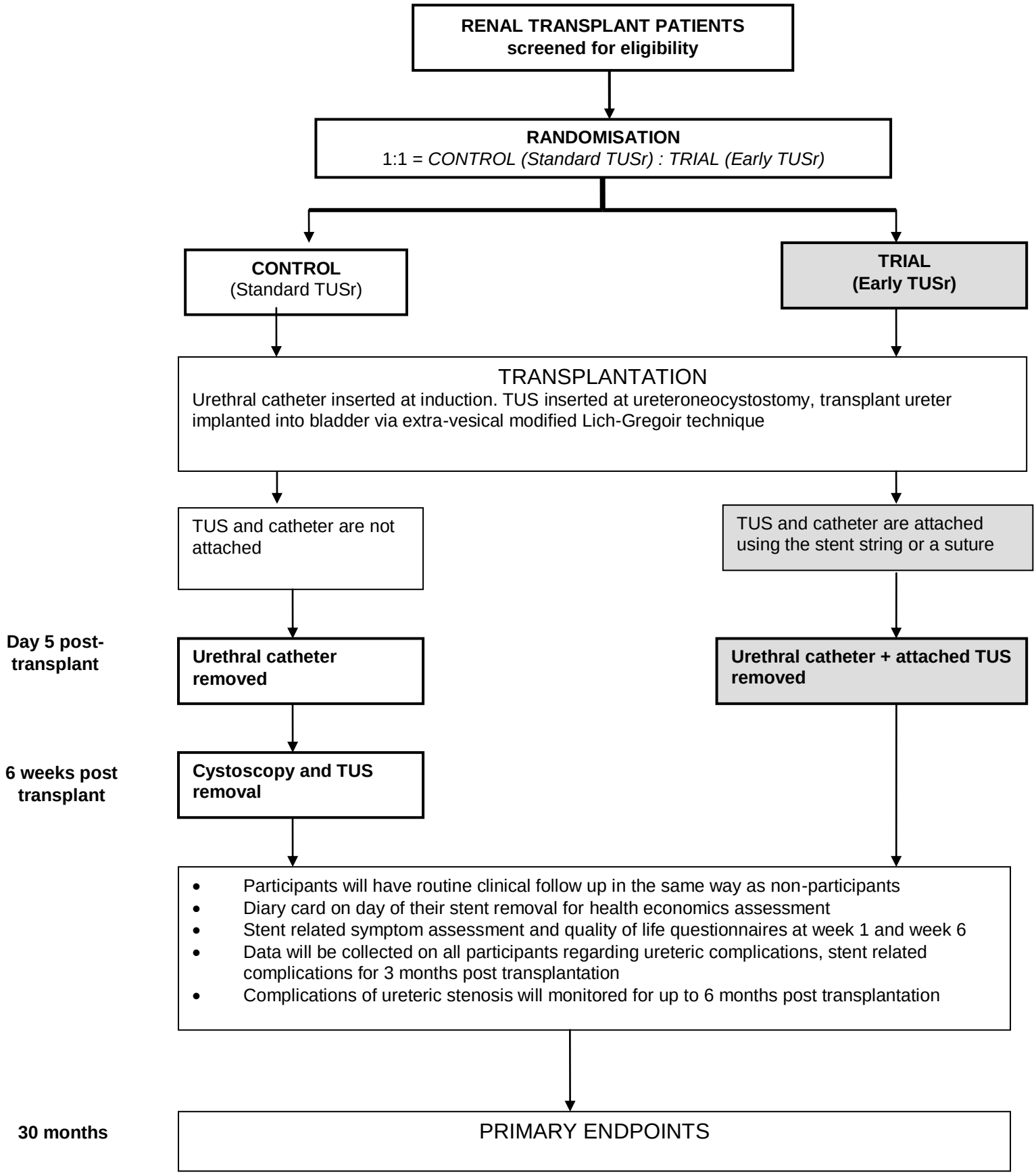
CONTENTS

1. STUDY SYNOPSIS

Title of clinical trial	Transplant ureteric stent removal: Early versus standard removal. A Randomised controlled trial.
Short Name	TrUST (Transplant Ureteric Stent Trial)
Sponsor name	Guy's and St Thomas' NHS Foundation Trust
Medical condition or disease under investigation	Renal Transplantation
Purpose of clinical trial	To determine if early transplant ureteric stent removal (eTUSr) leads to a decrease in stent related complications, specifically urinary infection, haematuria, pain and migration.
Primary objective	To determine the effect of early transplant ureteric stent removal (eTUSr) on stent related complication rates
Secondary objective(s)	To determine the effects of early TUS removal by new method on: 1. ureteric complication rates 2. patient acceptability 3. procedural costs 4. resource availability and allocation
Study Design	Randomised controlled trial
Study End-points	1. Stent complications monitored at each OPA for 3 months 2. Ureteric leak monitored at each OPA for 3 months 3. Ureteric stenosis monitored at each OPA for 6 months 4. Patient acceptability –QOL questionnaires at 1 & 6 weeks 5. Economic evaluation – diary card on day of stent removal, evaluation of hospital costs at 6 months
Sample Size	176 Renal Transplant Patients
Summary of eligibility criteria	1. Patients undergoing renal transplantation - Children aged 2 years and above - Adults
Summary of exclusion criteria	1. Urinary Tract exclusion: urinary diversion; pelvi-ureteric junction obstruction; surgical concern regarding the vascularity of the transplant ureter; donor kidney stone; early use of mTOR inhibitors 2. Increased risk of bleeding: post operative systemic heparinisation; >3 cycles of pre-operative plasma exchange (DFFP); kidney capsule removed at retrieval

	3. Simultaneous Kidney and Pancreas Transplant (SPK)
Investigational medicinal product and dosage	N/A; this is not a trial of an investigational medical product
Active comparator product(s)	N/A
Route(s) of administration	N/A
Maximum duration of treatment of a subject	N/A
Procedures: Screening & enrolment	All patients undergoing kidney transplantation will be considered for enrolment
Baseline	Baseline recipient data will be recorded.
Treatment period	The intervention is non-pharmacological. Patients will be randomised to one of two groups: control (conventional cystoscopic TUS removal) or trial (new method with early TUS removal), refer to flow diagram. Trial group will have their TUS attached to their catheter during surgery. Both Catheter and TUS will be removed on day 5 post surgery. The control arm will undergo catheter removal on day 5 and the current conventional method of cystoscopic TUS removal at week 6. Follow-up visits and tests are part of the transplantation protocol in the centres. Data will be obtained from the medical notes and local centre databases for up to 1 year
End of Study	Patients will be followed-up for 1 year
Procedures for safety monitoring during trial	**Complications will be reported to the Data Safety Monitoring Committee (DMC). The committee will meet in the 1st month & then at 3 monthly intervals.**
Criteria for withdrawal of patients on safety grounds	1. An increased rate of stent related complications in the eTUSr arm (>20%) 2. An increase in ureteric complications in the eTUSr arm (>1% urinary leak or >2 cases in the 1st month; 20% ureteric stenosis or >3 cases at 3 months) 3. Clinically and statistically different outcomes are shown in either arm and continuation of the study is considered unethical
Regulatory submissions on safety grounds	Not required as not a CTIMP

2. STUDY FLOW CHART



3. BACKGROUND

During kidney transplantation a plastic tube (stent) is placed in the transplant ureter, between the renal pelvis and the bladder. Meta-analyses of randomised controlled trials on the use of transplant ureteric stents (TUS) have shown that routine use of a TUS reduces major post transplant urological complications, particularly urinary leaks and ureteric stenosis [1, 2, 3].

The Current Problem:
However stent complications occur in around 20% of patients, both adults and children [4]. Studies suggest that TUS complications; which include urine infection, stent migration and pain; are related to the time stents remain in-situ [1, 2, 5]
The optimum timing for stent removal is currently not known, however a recent study suggested that stents should be removed at 2 to 4 weeks post transplantation [6]. In our centre we have reduced the time that our ureteric stents remain in-situ from 12 to 6 weeks post transplant on the basis of internal audit of transplant stent complications. Nevertheless, we continue to observe a 15-20% post transplant ureteric stent complication rate (internal unpublished audit); mainly of urinary infection and stent migration.

Most stent removal is performed under local anaesthesia by flexible cystoscopy, although a general anaesthetic cystoscopy is occasionally needed in adults and routinely in children. A novel technique of suturing the ureteric stent to the urethral catheter was described in 1998 [7]. This allowed the removal of both the stent and urethral catheter together without recourse to cystoscopy or anaesthesia. In this original description of the technique the urinary catheter/sutured ureteric stents were removed at a mean time of 8 days (range 6 to 10 days) [7]. A retrospective study of this technique in 590 patients showed it was safe and also reduced the urological complications seen without a stent [8]. In this study the urinary catheter/sutured ureteric stents were removed at a mean time of 10 days (range 8 to 12 days). A visit to the Mayo Clinic transplant unit by members of our transplant team observed the routine use of the novel technique to remove both urinary catheter/sutured ureteric stent on day 3 post renal transplant, but to our knowledge their practice has not been subjected to peer-review publication or prospective clinical trial.

Potential Benefits:
To patients: No need for a cystoscopy for stent removal. Patients are keen to avoid a second procedure (cystoscopy) for stent removal, as shown by a questionnaire carried out in our centre. With no required cystoscopy, patients and their relatives should benefit from reduced travel costs, work related problems, loss of income and time.
To patients and hospital: early stent removal with the new technique should decrease the incidence of stent related problems, especially urinary tract infection. This may decrease need for antibiotics, risk of antibiotic resistance and hospital admissions.
To hospital: The cost of outpatient flexible cystoscopy under local anaesthetic is around £766 per patient. Costs when general anaesthetic is required are considerably higher. This method will potentially free-up flexible cystoscopy resources to improve access for other patients requiring urgent diagnostic cystoscopy for bladder cancer.

Proposal:
A randomised controlled trial will compare the current standard TUS removal (sTUSr) to the novel technique with early TUS removal (eTUSr) at 5 days post transplantation. This will allow development of best clinical practice in this important area of early post kidney

transplant care. A urinary catheter is routinely placed into the bladder at the start of kidney transplant surgery. The optimal timing of urethral catheter removal post renal transplant has also not been defined but day 5 after surgery is the standard universally accepted day for catheter removal after kidney transplant surgery. Our unit removes the urethral catheter on day 5 post renal transplant. We do not leave the urethral catheter in the patient routinely longer than 5 days as this would be associated with increase risk of urinary infection.

The main design issue relates to the fact that in the intervention arm (eTUSr) there are 2 changes from current practice - earlier stent removal (day 5 rather than 6 weeks after surgery) and removal of stent together with catheter (rather than with cystoscopy). We wish to test eTUSr that allows removal of the stent together with the catheter so that patients benefit from not needing a cystocopy. Potentially this will be a huge benefit to patients. We have therefore chosen to remove the stent together with the catheter (in the eTUSr arm) on day 5 after surgery.

Our centre performs 200 kidney transplants per year, including the largest number of children in the UK. As an Academic Health Science Centre we are well-positioned to conduct clinical research. We have support from the Trust Research and Development Service, the London (South) Comprehensive Local Research Network (CLRN) and the Guy's and St Thomas' Biomedical Research Centre (BRC). Other UK transplant centres are potential trial collaborators.

4. TRIAL OBJECTIVES

The study has 4 main objectives:
1) To determine if early transplant ureteric stent removal (eTUSr) leads to a decrease in stent related complications
2) To determine the effect of eTUSr on ureteric complication rates (ureteric leak or stenosis)
3) To determine if eTUSr results in better patient acceptability
4) To determine if eTUSr leads to improved cost effectiveness

5. TRIAL DESIGN

5.1 Statement of Design

A randomised control trial evaluating the effect of early transplant ureteric stent removal to reduce stent related complications post renal transplant.

5.2 Study Population

Trial centres will include:
- Guy's and St Thomas NHS Foundation Trust (GSTT)
- The Evelina Children's Hospital (GSTT)
- Great Ormond Street Hospital for Children NHS Trust (GOSH)
- King's College Hospital (KCH)
- Kent & Canterbury (K&C)

Inclusion Criteria

- Children (age 2-16) needing kidney transplant
- Adults needing kidney transplant (17 – 75yrs)

Exclusion Criteria

- Urinary Tract exclusion:
  - urinary diversion e.g. *ileal conduit, cutaneous ureterostomy, mitrofanoff; duplex transplant ureter*
  - donor kidney pelvi-ureteric junction obstruction
  - donor kidney cyst with calyceal connection (increased risk urinoma)
  - surgical concern regarding the vascularity of the transplant ureter
  - donor kidney stone and use of bench (ex-vivo) ureteroscopy
  - early use of mTOR inhibitors (early use is very uncommon as the drug has well documented concerns regarding worse tissue healing)
- Risk of bleeding:
  - kidney capsule removed at retrieval
  - need for post operative systemic heparinisation
  - >3 cycles of pre-operative plasma exchange (DFFP) as part of transplant desensitisation program
- Simultaneous Kidney and Pancreas Transplant (SPK)

5.3 Number of Subjects

We estimate a sample size of 176 patients will need to be recruited

5.4 Recruitment Process

Patients will be informed of the trial at pre-transplant education sessions so that they will be familiar with the study when they are formally invited to participate at the time of admission for kidney transplant surgery. They will be given patient information leaflets and the trial will be explained in concordance with Good Clinical Practice (GCP). All data will be held in concordance with GCP. Following informed written consent patients will be randomised into one of the 2 study arms.

5.5 Sample Size Determination

An audit over the last 3 years has demonstrated that between 15 to 20% of patients have TUS-related complications, mainly UTI in the first 3 months post transplant surgery. On this basis, we aim to reduce our TUS-related complication rate to a target rate of 5%. Statistical power calculations were performed by Prof Grieve, Statistician, KCL, London. Based on a chi-squared test with 80% Power and a 5% 2-sided type I error rate 88 patients per group are required assuming a current 20% TUS-related complication rate. The corresponding number is 160 patients per group assuming a current 15% TUS-related complication rate.
As there is a degree of uncertainty in the starting TUS-related complication rate, we will perform a sample size re-estimation based on predictive power after 25 patients per group which we anticipate will be 3 months into the trial.

5.6 Randomisation

Online randomisation system provided by the Mental Health and Neurosciences Clinical Trials Unit, King's College London. Recruits will be randomly allocated in a 1:1 ratio to standard TUS removal (cystoscopic removal at 6 weeks) and early TUS removal (on day 5 with catheter). Randomisation type is stratified block randomisation with randomly varying block sizes. Stratification is for age - adult or child.

5.7 Study Objectives

Primary Objective
To determine the effect of early TUS removal on the incidence of stent related complications (namely pain, haematuria, urinary tract infection, migration and fragmentation)

Secondary Objectives
To determine the effects of early TUS removal by attaching the stent to catheter on:
1. ureteric complication rates
2. patient acceptability
3. procedural costs
4. resource availability and allocation

5.8 Study Endpoints

Primary Endpoint
Incidence of stent related complications (composite endpoint) in each arm

Secondary Endpoints
1) Incidence of ureteric leak at 3months post transplantation for each arm
2) Incidence of ureteric stenosis at 6 months post transplantation for each arm
3) Quality of life assessment using FAIT-U and EQ-5D at week 1 and week 6 post transplant
4) Patient completed diary cards (day of stent removal)
5) NHS reference costs for stent removal procedure and management of stent related complications at 6 months.

5.9 Trial Treatments

The study is a randomised control trial in which there are two potential study arms to which patients are randomly allocated, see below. It is not possible to blind patients or investigators as to whether they will undergo the standard technique or the novel technique for stent removal due to noticeable differences in the method of procedure.

Group 1: CONTROL - Standard technique for TUS removal (sTUSr)
Group 2: TRIAL - Novel technique with early TUS removal (eTUSr)

A TUS is placed at the time of surgery along with a urinary catheter in all patients. Patients in Group 1 will have the urinary catheter removed on the ward on the 5th post-operative day. They will then undergo a cystoscopy, under either local or general anaesthetic, at week 6 to remove the TUS. Cystoscopy and stent removal takes

approximately 10 minutes. Patients will be given a prophylactic intravenous injection of antibiotic to cover the procedure. Patients in Group 2 will have the TUS attached to the urinary catheter at the time of surgery. These patients will have the urinary catheter removed on the ward on the 5th post-operative day in the standard way. As the TUS is attached to the catheter it will be removed at the same time as removal of the catheter. Catheter removal simply involves deflating the catheter balloon to allow it to slide out from the bladder. It is a non-invasive procedure that does not cause discomfort or risk to the patient. Removing the catheter with the stent attached will not change this. Group 2 therefore do not require cystoscopy.
The study will be performed prospectively. Patients that require kidney transplantation will be recruited and allocated to a study arm. Participants of the study will have routine clinical follow up in the same way as non-participants. A diary card will be completed by both trial groups on the day of their stent removal. Stent related symptom assessment and quality of life questionnaires will be completed by all adult participants at week 1 and week 6. Data will be collected on all participants regarding ureteric complications, stent related complications, health economics and patient quality of life assessments for 3 months post transplantation. Complications of ureteric stenosis will monitored for up to 6 months post transplantation.

5.10 Surgical Technique

All surgeons perform the transplant ureter / bladder anastomosis using an extra-vesical technique (modified Lich-Gregoir Technique). All patients have a double J stent (Cook Medical) and a urethral catheter inserted. It is advantageous but not essential to tape the external section of the bladder catheter to the patient's thigh to maintain its position in the bladder to increase ease of locating the catheter tip intra-operatively.
In patients randomised to eTUSr the ureteric stent will be attached to the "eye" of the urethral catheter. This should be done by passing the "string" attached to the stent through the "eye" of the urethral catheter and tying a knot to secure the "string" to the catheter. An acceptable alternative is to pass a non-absorbable suture through both the lower end of the stent and the "eye" of the urethral catheter.

5.11 Cystoscopic Stent Removal

All patients will have urine dipstick testing and MSU sent for MC&S prior to cystoscopic stent removal. For patients without UTI symptoms and with a normal urine dipstick result cystoscopy should be covered with a single dose antibiotic chosen according to local practice.

Where either there is a positive dipstick for nitrites or the presence of UTI symptoms the following possible scenarios are all acceptable:

- Lower urinary tract symptoms but dipstick test is nitrite negative - proceed as above but may also require oral antibiotics post procedure for 3-5 days (follow local guidelines for antibiotic prescribing).
- Dipstick positive for nitrites +/- lower urinary tract symptoms, but no systemic features - proceed to stent removal with antibiotic cover as above. Oral antibiotics may also be prescribed post procedure for 3-5 days (follow local guidelines for antibiotic prescribing).

- Dipstick positive & upper urinary tract symptoms or systemic features of infection – consideration of delaying stent removal for up to 48 hours to permit antibiotic treatment for 48 hours prior to proceeding with stent removal The procedure should be covered with appropriate antibiotics and antibiotics continued for a further 7 - 14 days.
- If there is a prior positive culture on MSU – antibiotics may also be prescribed prior to stent removal and continued post procedure for 3-5 days.

6. EXPERIMENTS/LABORATORY TESTS

6.1 Microbiology Experiments

This study provides a unique opportunity to link "state of the art" molecular diagnostics of infection with the potential to increase our knowledge of urinary tract infection in this setting. A subset of transplant ureteric stents from each group, once removed from the patient, will be analysed by confocal laser microscopy to assess for bacteria in patients both with and without defined urinary tract infection. The stents will be orientated and differences in the bacteria (number or type) in the proximal (kidney) versus distal (bladder) ends will be assessed. Biofilms will be quantified by confocal microscopy [10] using Dead/Live stain (Molecular Probes) and the presence and distribution of specific pathogens especially Enterococcus faecalis [11] will be determined using species-specific probes with fluorescent in situ hybridization (FISH).
These molecular techniques will provide an additional level of information relating to TUS infection. They will permit comparison to standard urine culture and assess whether there are particular sites on the stents that bacteria tend to colonise. This work will be conducted in collaboration with Prof David Beighton, King's College London, using the core imaging facilities of KCL. Descriptive statistics and estimates of differences between groups will be determined with 95% confidence intervals.

7. DATA ANALYSIS

The primary outcome is stent related complication rates and the two study arms will be compared against each other. For the primary end-points a stratified Mantel-Haenszel test will be used. The secondary outcomes are: ureteric complication rates, economic costs, stent related symptoms and quality of life scores. For secondary endpoints analysis of covariance will be used for continuous endpoints, unless there is evidence that the assumption of normality is untenable in which case a stratified Wilcoxon test will be used. For dichotomous data a stratified Mantel-Haenszel test will be used.

Each treatment arm will be considered in terms of costs divided by quality-adjusted life year (QALY) and also incremental cost effectiveness ratio (ICER). QALYs will be derived from facit (FAIT-U) and EQ-5D questionnaires. Health economic evaluations will be made in collaboration with Prof A McGuire, London School of Economics.

All analyses will be stratified by age. Given our patient population for the study (see below) we will stratify randomisation into paediatric (less than 16 years old) and adult populations. As urinary tract causes of renal failure are higher (~25%) in children

compared with adults (~ 5%), this stratification will also cover the majority of patients at higher risk of UTI.

7.1 TUS-related complication definitions:

Complications are defined as occurring in first 3 months post transplant except transplant ureteric stenosis which can develop insidiously and so will be recorded for the first 6 months post transplant.

- Urinary Tract Infection (UTI) - microbiology (MC&S) in the early (<3month) post transplant setting
  - Symptomatic - dysuria / fever / pain over transplant or native kidneys with Mid Stream Urine (MSU) culture bacteria > 10^{x2} with pyuria
  - Asymptomatic - Mid Stream Urine (MSU) culture bacteria > 10^{x5} with pyuria
- Stent migration - ultrasound and / or plain x-ray diagnosis of TUS not appropriately positioned (coils not in both the transplant renal pelvis and the bladder).
- Stent pain – requiring stent removal
- Haematuria – frank haematuria requiring catheterisation +/- irrigation
- Stent Fragmentation

Urological complications definitions:

- "Urinary leak "- Transplant Uretero-neocystotomy anastomotic leak - diagnosed by biochemical confirmation (creatinine level of transplant drain fluid); radiological evidence on cystogram; intra-operative assessment with intra-vesical methylene blue testing.
- Transplant ureteric stenosis - diagnosed with radiological evidence using antegrade nephrostogram (pyelo-ureterogram).

7.2 Follow-up schedules and requirements

Patients in the eTUSr group who have urethral catheter / stent removed earlier or later than Day 5 post operation will have the reason clearly documented in medical notes. The post-operative day urethral catheter / stent removed will be clearly recorded.
Patients in the sTUSr group will have the TUS removed in week 6 post transplant. Patients who have TUS-related complications that warrant TUS removal before 6 weeks will have the reason clearly documented in medical notes. The post-operative day the TUS is removed will be clearly recorded. If for administrative reasons (such as availability of cystoscopy list) TUS removal is earlier or later than 6 weeks the reason clearly documented in medical notes.

Urine samples will be collected routinely (current clinical practice) as follows:

- At admission for transplant: in patients who pass urine - MSU for MC&S (microscopy, culture and sensitivity)
- Prior to urethral catheter removal - day 5 - CSU (catheter specimen urine) for MC&S
- At each transplant outpatient clinic midstream urine samples are dipstick tested. Abnormal results on dipstick test are sent for MC&S. Month 1: 3 visits/ week; Month 2: 2 visits/ week; Month 3: 1 visit / week.

- Prior to cystoscopic removal of TUS - MSU for dipstick and MC&S (microscopy, culture and sensitivity)

Health economics:

- Assessment of costs of eTUSr versus sTUSr.
  - Hospital costs assessed by NHS reference costs.
  - Patient costs by self-completed diary cards and will include both direct costs (expenditure) and indirect costs (e.g. loss income).

Patient satisfaction:

- Quality of Life assessment (using FAIT-U, version 4.0 and EQ -5D) will be carried out by adult participants in both treatment arms.

8. ETHICAL CONSIDERATIONS

8.1 Potential Benefits

Kidney transplantation is the most economic form of renal replacement therapy and compared to dialysis is the preferred treatment for most patients. However, there are side-effects and potential complications related to transplantation. It is important to direct our efforts to minimise them. This study aims to address specific post-operative urinary tract complications including infection associated with the routine use of transplant ureteric stents.

The potential value of this research will be to determine which approach has:

- Lowest urinary tract infection rates
- Lowest urinary tract complication rates
- Better patient acceptability
- Better cost effectiveness (health economic outcome)

8.2 Potential risks

There is the potential for unexpected complications in the new technique arm of the study. These may be related to the early removal of the stent on the 5th post operative day.

- The main potential complication is an increase in the urinary leak rate (>1%). This would be clinically detectable by a decrease in voided urine volume and discomfort around the transplanted kidney. Investigation would be with an ultrasound scan. Treatment would be with replacement of the urinary catheter for 2 weeks and a cystogram before removal. Any incident of urinary leak in either group would be immediately reported to the Trial Data Safety Monitoring Committee. An increase incidence in urinary leak rates (>2 cases in the first month) in either arm would trigger a trial safety review and if necessary temporary cessation in the study until appropriate clinical review. However, data to date from the literature [6, 7] and personal communications (The Mayo Clinic, 2006) suggest no increase in urinary leak complication rate with the new technique.
- There is the potential that we find an increase rate (>15-20%) of ureteric stenosis in the early (3 month) post transplant period. This would present with a decrease in void volume, discomfort around the transplant or deteriorating renal function.

Investigation would involve an ultrasound scan and be initially managed with either nephrostomy or retrograde insertion of ureteric stent. Nephrostogram / retrograde x-ray would be obtained to confirm diagnosis. Treatment would involve either endo-urological or an open corrective surgical approach. >3 cases of stenosis in the first 3 months would generate trial review. Data to date does not suggest increased complications of stenosis with early removal of ureteric stents.

- There is the potential for a short increase in the operating time during kidney transplant surgery. We anticipate that the new technique of suturing the stent to the catheter will add between 5 to 10 minutes to the overall surgery time of approximately 3 hours (however this can vary between 2-6 hours depending on complexity of case). Operating time data is routinely collected from all surgery (Galaxy System). Any unforeseen problems will be notified to the Trial Data Safety Monitoring Committee. Mean operating times over 3 monthly periods will be assessed between trial groups. A significant increase (> 1 hour) difference in mean operating times would trigger a trial safety review and if necessary temporary cessation in the study until appropriate clinical review.

This study has been reviewed and given favourable opinion by Guy's Hospital Research Ethics Committee and additionally has been passed by the Renal Project Board of Guy's Hospital.

We will ensure that our participants are fully informed of the potential risks and benefits before they are able to enter the trial. Trial information will be given at pre-transplant education sessions by both a researcher and a member of the direct care team. Information leaflets will be provided and are adapted to individual age groups. Adequate time to consider the information and ask questions before making a decision will be given to all potential participants.

8.3 Data Protection

All data collected in the study will be anonymised and stored on a password protected computer or on password protected memory sticks. All data will be stored and archived within the Guy's and St Thomas' renal transplant department archive in line with the Joint Clinical Trials Archiving recommendations.

8.4 Data Monitoring Committee

There will be not be a separate Trial Steering Committee, but the Trial will be overseen by the Data Monitoring Committee below.
Committee Chair: Dr Marlies Ostermann (Consultant in Nephrology, GSTT)
Members: Mr Geoff Koffman (Consultant in Renal Transplantation, GSTT and co-applicant) Mr Shamim Khan (Consultant in Urology, GSTT); Ms Penny Mawson (Head of Clinical Governance GSTT Renal Department); Mr Jonathon Olsburgh (Consultant in Renal Transplantation GSTT and lead applicant); Dr Manish Sinha (Consultant Paediatric Nephrologist, Evelina Children's Hospital, GSTT); Professor Janet Peacock (Professor of Medical Statistics, King's College London), Dr Irene Rebollo-Mesa (Research Fellow in Biostatistics and Bioinformatics, MRC centre for transplantation); Miss Pareeta Patel (Clinical Research Fellow in Urology, GSTT).

The committee will assess trial progress, occurrence of adverse events and other aspects of the trial such as recruitment. The committee will meet in the 1st month & then at 3 monthly intervals.
The trial will be stopped if in the opinion of the Data Monitoring Committee the following conditions have been satisfied:

An increase rate of stent related complications in the eTUSr arm (>20%)
An increase in ureteric complications in the eTUSr arm (>1% urinary leak or >2 cases in the 1st month; 20% ureteric stenosis or >3 cases at 3 months)
Clinically and statistically different outcomes are shown in either arm and continuation of the study is considered unethical.

8.4.1 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets, X-ray reports, microbiology reports etc).

8.4.2 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained by the Joint Clinical Trials Office Quality Team.

9. PROJECT TIMESCALE

Our subject population appear to be motivated to be engaged and enrol in clinical research. In other studies in our unit over 75% of patients asked to participate in clinical research consent to be involved. We therefore believe that the required patient numbers on initial estimation (176) is achievable in 2 years given our transplant activity. If after our sample re-estimation the patient number required is higher (320), then we would need to recruit other centres to the trial. Other UK centres (such as Royal Free and Newcastle) have already expressed an interest to collaborate with us.

10. SPONSORSHIP

Guy's & St Thomas' NHS Foundation Trust, Guy's Hospital, BRC, 16th Floor Tower Wing, St Thomas Street, London, United Kingdom. SE1 9RT

11. DISSEMINATION AND OUTPUT

It is intended that results will be published in peer reviewed medical journals and presented within the trust and at conferences externally. The results will be available to participants of the research study and transplant patients in the form of a leaflet if they wish. Results will also be sent to the local Kidney Patient's Association.

12. PUBLICATION POLICY

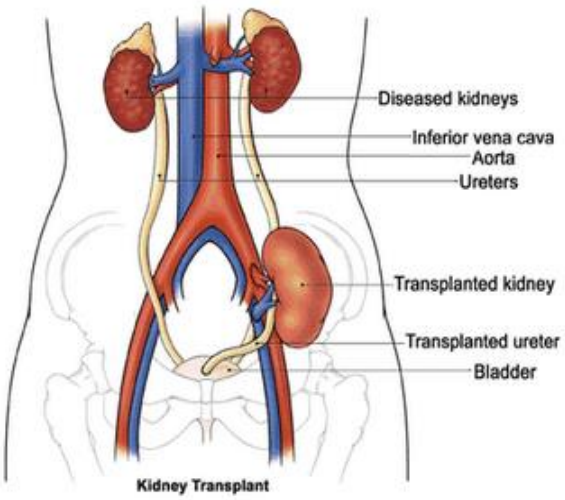
All data collected in this study is the intellectual property of the investigators

who should be included in the authorship of any presentation or publication of data as under international copyright laws.

13. APPENDICES

A: Schematic diagram of the kidney transplant procedure and a ureteric stent.

Transplantation Procedure Diagram:
The donor kidney must be transplanted within 24-28 hours of removal from the donor. It is transplanted into the pelvic area and the donor kidney blood vessels are connected (anastomosed) to the recipient's blood vessels. The donor ureter is implanted into the bladder.

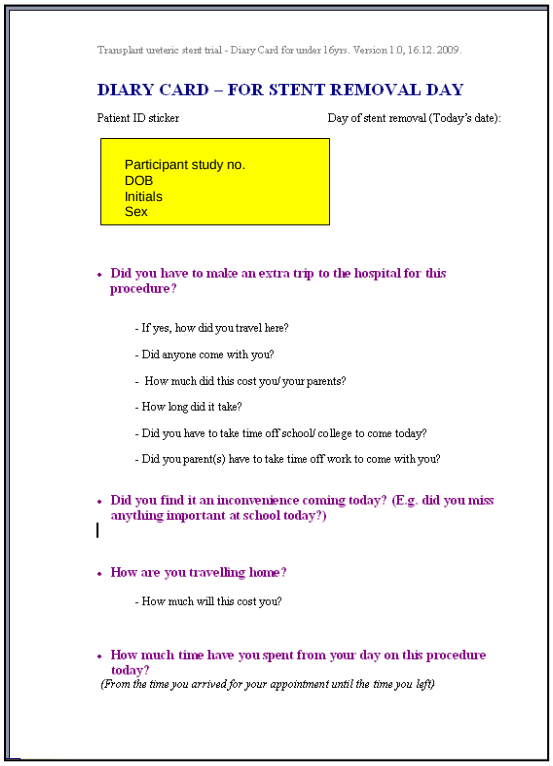


The Transplant Ureteric Stent:
This is placed in the transplant ureter with one end in the kidney and the other in the bladder. Diagram is approximately life size.

B: Questionnaires to be used in the study

- Diary Cards for health economics assessment
- Quality of life validated questionnaires
  - FAIT-U (factit.org)
  - EQ-5D (EuroQol)

Children's diary card



Transplant ureteric stent trial - Diary Card for under 16yrs. Version 1.0, 16.12. 2009.

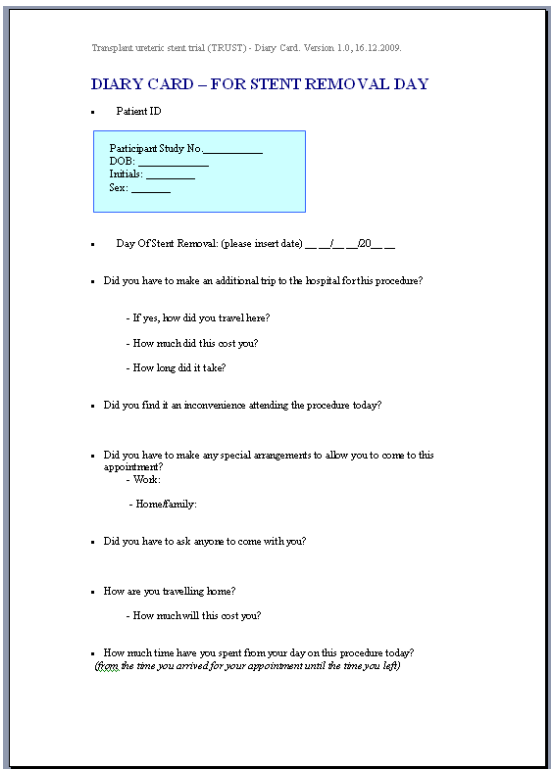
DIARY CARD – FOR STENT REMOVAL DAY

Patient ID sticker Day of stent removal (Today's date):

Participant study no.
DOB
Initials
Sex

- **Did you have to make an extra trip to the hospital for this procedure?**
  - If yes, how did you travel here?
  - Did anyone come with you?
  - How much did this cost you/ your parents?
  - How long did it take?
  - Did you have to take time off school/ college to come today?
  - Did you parent(s) have to take time off work to come with you?
- **Did you find it an inconvenience coming today? (E.g. did you miss anything important at school today?)**
- **How are you travelling home?**
  - How much will this cost you?
- **How much time have you spent from your day on this procedure today?**
  (From the time you arrived for your appointment until the time you left)

Adult's diary card



Transplant ureteric stent trial (TRUST) - Diary Card. Version 1.0, 16.12.2009.

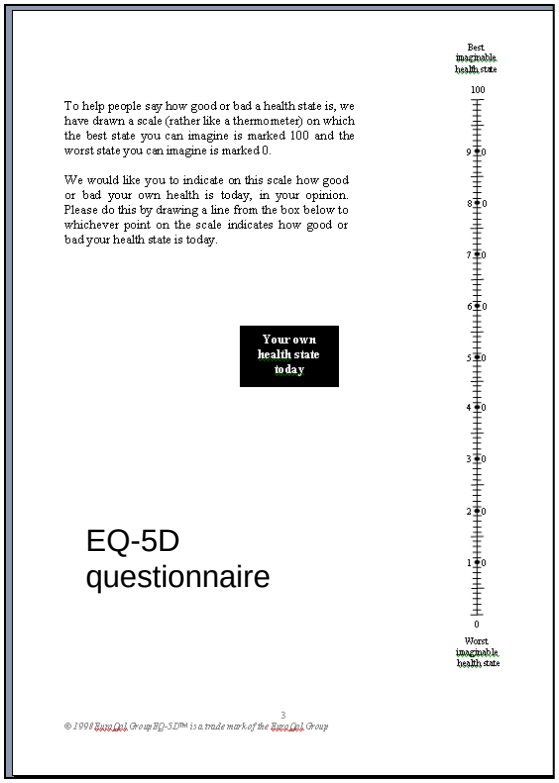
DIARY CARD – FOR STENT REMOVAL DAY

- Patient ID

Participant Study No._____
DOB: _____
Initials: _____
Sex: _____

- Day Of Stent Removal: (please insert date) __ __/__ __/20__ __
- Did you have to make an additional trip to the hospital for this procedure?
  - If yes, how did you travel here?
  - How much did this cost you?
  - How long did it take?
- Did you find it an inconvenience attending the procedure today?
- Did you have to make any special arrangements to allow you to come to this appointment?
  - Work:
  - Home/family:
- Did you have to ask anyone to come with you?
- How are you travelling home?
  - How much will this cost you?
- How much time have you spent from your day on this procedure today?
  (from the time you arrived for your appointment until the time you left)

QoL Questionnaires: Adults only (≥17 years)



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Best imaginable health state
100
90
80
70
60
50
40
30
20
10
0
Worst imaginable health state

3

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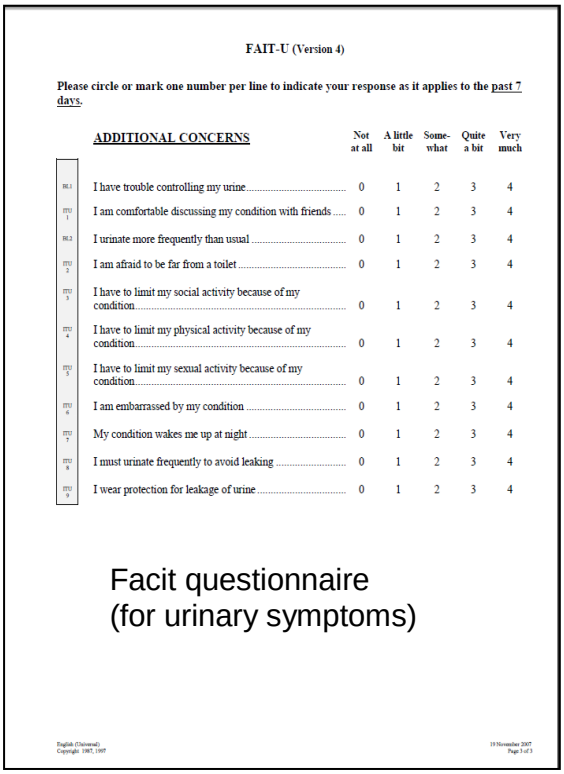
EQ-5D questionnaire



FAIT-U (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine	0	1	2	3	4
FTU 1	I am comfortable discussing my condition with friends	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
FTU 2	I am afraid to be far from a toilet	0	1	2	3	4
FTU 3	I have to limit my social activity because of my condition	0	1	2	3	4
FTU 4	I have to limit my physical activity because of my condition	0	1	2	3	4
FTU 5	I have to limit my sexual activity because of my condition	0	1	2	3	4
FTU 6	I am embarrassed by my condition	0	1	2	3	4
FTU 7	My condition wakes me up at night	0	1	2	3	4
FTU 8	I must urinate frequently to avoid leaking	0	1	2	3	4
FTU 9	I wear protection for leakage of urine	0	1	2	3	4

English (Universal)
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Facit questionnaire
(for urinary symptoms)

14. REFERENCES

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